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An Enantioselective Total Synthesis of Tremulenediol A and Tremulenolide A and Development of the $[Rh(CO)_2Cl]_2$-Catalyzed Direct, Stereoselective Allylic Alkylation of Unsymmetrical Substrates

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by

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Dedication

This dissertation is dedicated to the one person who stood by me with undying support throughout the course of this work. Helping in more ways than I could have imagined. All the while constantly reminding me to breathe.

To my loving wife, Leea

Acknowledgements

Special thanks goes first and foremost to my Mom and Dad who, without their constant encouragement, I may not have been able to achieve nearly as much as I have. I would also like to thank Professor Stephen F. Martin for the guidance and support that he has given me throughout this journey. For introducing me to the science of synthetic chemistry and mentoring me through my early years as a scientist I thank Dr. Andrew S. Judd and Professor Thomas R. Hoye. Finally I would like to thank my fellow Martin Group members, both past and present, with which I have had the distinct honor to call my coworkers. Without the guidance, support and overall friendship of my colleagues at the University of Texas at Austin I would not be the chemist or the person I am today.

An Enantioselective Total Synthesis of Tremulenediol A and Tremulenolide A and Development of the $[Rh(CO)_2Cl]_2$-Catalyzed Direct, Stereoselective Allylic Alkylation of Unsymmetrical Substrates

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A method for the enantioselective construction of the [5.3.0] bicyclic carbon skeleton present in the tremulane sesquiterpenes is described. The route incorporates an enantioselective rhodium(II)-catalyzed intramolecular cyclopropanation that sets the stage for a diastereoselective rhodium(I)-catalyzed [5+2] cycloaddition as an efficient approach to the tremulane natural products tremulenediol A and tremulenolide A. The use of rhodium(I)-catalyzed carbocyclization and allylic alkylation transformations was likewise explored. To that end, a novel regio- and stereoselective $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation of unsymmetrical allylic carbonates was discovered. The regioselectivity favors product ratios in which the major product arises from substitution

at the carbon that previously bore the allylic leaving group by the malonate nucleophile. When an enantiomerically enriched carbonate (≥ 99% *ee*) was examined, the Rh(I)-catalyzed allylic alkylation proceeded stereoselectively to provide the alkylation product with retention of absolute stereochemistry (98% *ee*).

To establish the scope of the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation, a variety of carbon and heteroatom nucleophiles were examined and the results described. A series of unsymmetrical allylic carbonates were treated with the sodium salts of various substituted malonates, □-ketoesters and sulfones in the presence of $[Rh(CO)_2Cl]_2$ to provide the corresponding direct substitution products in good yield and with excellent regioselectivity. Preliminary studies were conducted to include allylic etherifications utilizing sterically hindered phenols and aminations of unsymmetrical carbonates with *N*-alkylated sulfonamides.

As an application of the rhodium(I)-catalyzed allylic alkylation, a series of novel domino reactions have been invented that involve the regioselective and stereoselective $[Rh(CO)_2Cl]_2$-catalyzed alkylation of allylic trifluoroacetates with the □-substituted sodiomalonates followed by either an intramolecular Pauson-Khand annulation, a cycloisomerization, or a [5+2] cycloaddition. A unique aspect of the method described is the use of a *single* catalyst to effect sequential transformations in which the catalytic activity is moderated simply by controlling the reaction temperature. This strategy thus provides a rapid and efficient entry into a variety of bicyclic carbon skeletons.

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Chapter 1. Transition Metals in Organic Synthesis

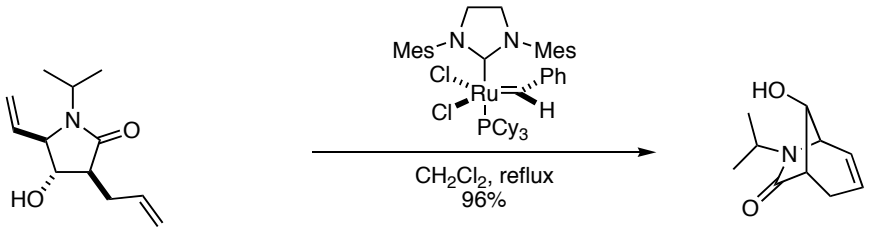
1.A INTRODUCTION

Over the past century, organic synthesis has evolved into one of the key scientific disciplines responsible for technological advances ranging in scope from materials to biological sciences. Although the development of synthetic methods continues to modernize the science which thereby contributes significantly to the standard of living enjoyed by much of the world today, organic synthesis is far from being fully developed. Issues receiving increased attention as of late to further advance the organic chemistry include atom economic transformations and optimizing synthetic efficiency. These efforts have focused primarily on utilizing transition metal catalysts to facilitate usually indiscriminate or unconventional reaction processes to proceed in a selective facile manner. Through the use of transition metals to mediate organic reactions, one can stabilize otherwise highly reactive intermediates thereby rendering them efficient synthetic reagents, alter normal reactivity patterns of functional groups by making nucleophilic species electrophilic and vice versa, and allow for unprecedented selectivity to obviate the need for wasteful chiral auxiliaries or inefficient protection-deprotection sequences.

A number of transition metal-catalyzed processes have been extensively developed over past few decades to the point at which one would be hard pressed to devise a concise synthesis of a complex target without employing at least one if not more of these reactions. Just a representative few are illustrated below in Eqs. 1a.1 and 1a.2. In 2003, Martin and coworkers illustrated the use of the ruthenium-catalyzed ring closing metathesis reaction to arrive at a formal synthesis of the indole alkaloid (–)-peduncularine (Eq. 1a.1).[1] Treatment of lactam **1a.1** with Grubb's second generation olefin metathesis

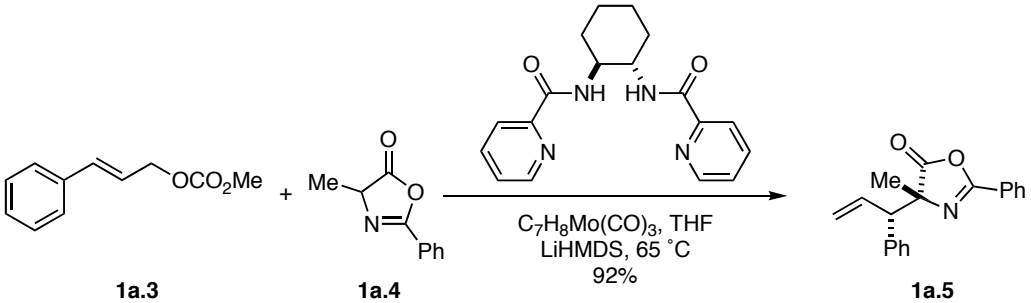
catalyst provided the bridged bicycle **1a.2** in 96% yield that was an intermediate in Speckamp's synthesis of the target indole (Eq. 1a.1). Transition metal-catalyzed allylic alkylations represent one of the most prevalent transformations mediated by a metal catalyst. In 2002, Trost and coworkers illustrated the use of a molybdenum-catalyzed asymmetric allylic alkylation of carbonate **1a.3** with the enolate of azalactone **1a.4** to provide quaternary amino acid precursor **1a.5** (Eq. 1a.2).[2] In fact, if one peruses the literature, few total synthesis reports do not include at least a few reactions in which a transition metal species is used.

Ring Closing Metathesis



1a.1 **1a.2** (1a.1)

Asymmetric Allylic Alkylation



1a.3 **1a.4** (1a.2)

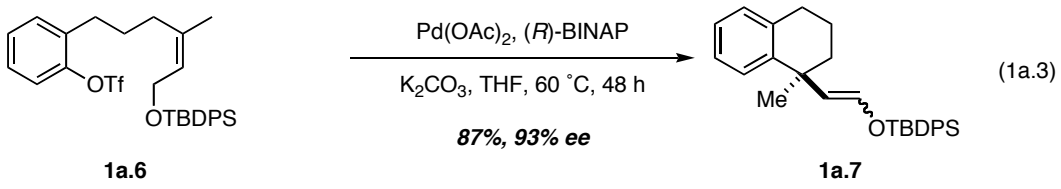
dr = 97:3; ee = 99%

1a.5

The use of palladium has revolutionized the field of transition metal catalysis. The Heck reaction has become a staple in synthetic chemistry with Overman's group pioneering the development and utilization of the asymmetric Heck reaction in total

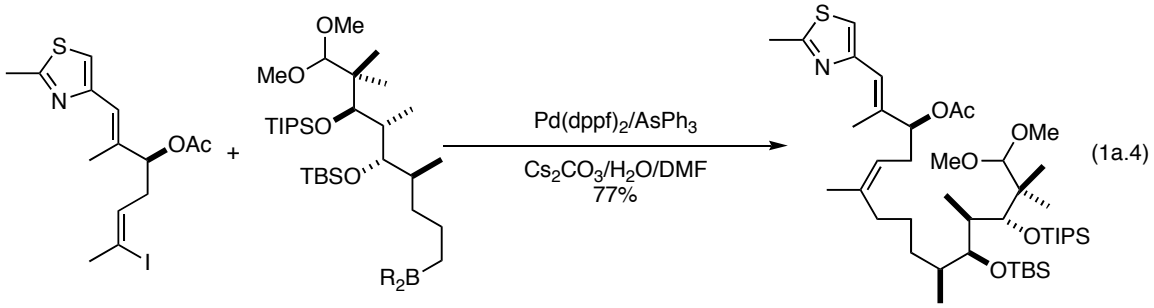
synthesis. As illustrated in Eq. 1a.3, treatment of aryl triflate **1a.6** with $Pd(OAc)_2$ in the presence of (*R*)-BINAP provided silyl enol ether **1a.7** in 93% *ee*.[3] Palladium catalysis has also found increased use in cross-coupling reactions such as the Stille and Suzuki couplings. For example, treatment of vinyl iodide **1a.8** with $Pd(dppf)_2$ and alkyl boronate **1a.9** yielded the cross-coupling product **1a.10** in 77% yield.[4] These examples illustrate a very limited sampling of the recent advances in transition metal catalysis in recent decades.

Asymmetric Heck Reaction



1a.6 **1a.7** (1a.3)

Suzuki Cross-Coupling



1a.8 **1a.9** **1a.10** (1a.4)

With the multitude of advances made on transition metal chemistry, so much is still not well understood. Due to the myriad of potential mechanisms for many processes, understanding reaction pathways to accurately predict product formation and/or selectivities associated with their formation can at times be an impossible task. The involvement of reaction intermediates and pathways of similar energies further

complicates the analysis. However, these observations can be viewed as an unprecedented opportunity in organic synthesis. Transition metals can provide alternative reaction pathways through small modifications of the catalytic species, and even allow for entirely new reaction mechanisms untenable through traditional synthetic methods. In proceeding sections, this discussion will focus on the realm of allylic alkylations and ring forming reactions as a backdrop to future chapters. No matter the role of the chemist in synthesis, the use of transition metal catalyst will, of the foreseeable future, play a critical part in complex molecule synthesis.

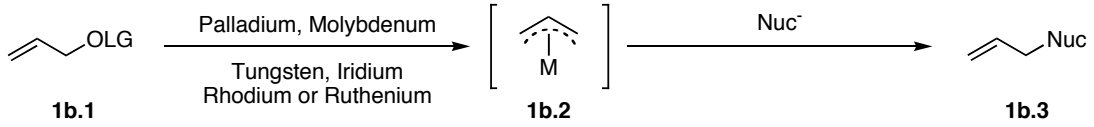
1.B TRANSITION METAL-CATALYZED ALLYLIC ALKYLATIONS

1.B.1 Introduction

Few transition metal-catalyzed transformations in recent years, have gained as much attention or been so frequently employed in the synthesis of complex molecules of biological significance as the allylic alkylation reaction.[5] Such reactions have arguably changed the face of organic synthesis. Beginning in the mid-1970's, the allylic alkylation[6-13] has been studied for its synthetic utility, and its mechanism has been elucidated through a variety of studies and experimental observations. The general process involves oxidative addition of the metal catalyst to an allyl substrate **1b.1** to yield an intermediate π-allyl metal intermediate **1b.2** that undergoes nucleophilic addition to provide the alkylated product **1b.3**. Gradual trends, such as the ever-increasing focus on asymmetric processes, in organic synthesis have also played a role in the evolution of transition metal-catalyzed allylic alkylations. More recently the main thrust of work in the area has been toward enabling enantioselective capabilities. As the nature of organic synthesis has changed from the construction of complex molecules to their *asymmetric*

assembly, so too has the transition metal-catalyzed allylic substitution reaction been rendered enantioselective through the use of chiral ligands on the metal center. Although a number of reactions have seen their utility explode by the development of asymmetric variants, few can say that they have achieved the hierarchal position that the asymmetric transition metal-catalyzed allylic alkylation enjoys.

Scheme 1b.1



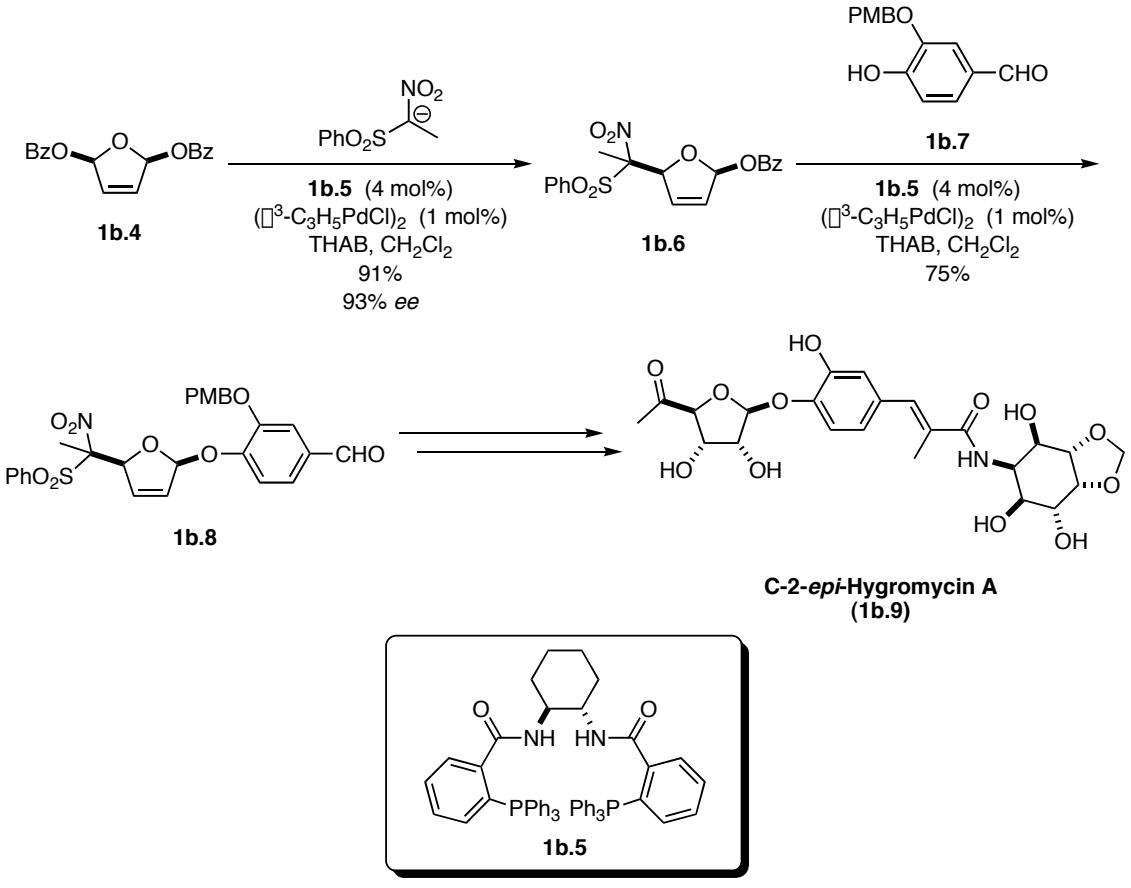
1b.1 **1b.2** **1b.3**

What has really established the metal-mediated allylic alkylation as a cornerstone reaction in the organic chemists synthetic toolbox is its versatility. The scope has expanded through the plethora of allylic substrates and nucleophiles and the discovery that a number of different transition metals are capable of mediating the transformation. The differences in catalytic activity that each metal exhibits range from subtle to dramatic. The factors that influence one catalytic species to direct the regio- and stereochemical outcome of the substitution reaction may yield an entirely different result when a different metal complex is employed. The exploitation of these various selectivity trends in the synthesis of complex molecules has been one of the primary factors in establishing the transition metal-catalyzed allylic alkylation as a force in the synthesis of biologically significant natural products.

The asymmetric synthesis of C-2-*epi*-hydromycin A (**1b.9**) (Scheme 1b.2) provides a glimpse at the nucleophilic diversity of the palladium-catalyzed allylic alkylation. Asymmetric allylic alkylation of *meso*-bisbenzoate **1b.4** in the presence of ligand **1b.5** provided the *syn* substitution product **1b.6** in 91% yield and 93% *ee*.[14]

Immediately following this substitution reaction, allylic etherification with phenol **1b.7** provided ether **1b.8** in 75%.[15] Although this reaction was performed in the presence of a chiral ligand, the inherent diastereoselectivity in the palladium-catalyzed allylic substitution reaction, which will be discussed later, would have still provided the desired adduct stereoselectively. However, at times the palladium species generated *in situ* by the presence of chiral ligands exhibits enhanced reactivity, thereby making it the catalyst of choice for the desired substitution reaction.

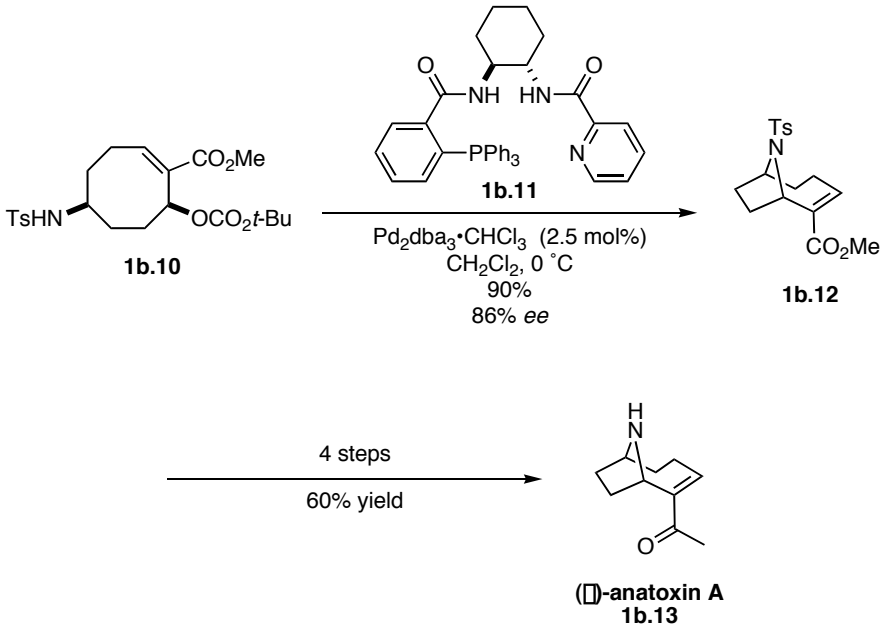
Scheme 1b.2



Heteroatom nucleophiles were used to further illustrate the scope and utility of the transition metal-catalyzed allylic alkylation reaction. As depicted in Scheme 1b.3, the

intramolecular asymmetric allylic amination of racemic sulfonamide **1b.10** with the sterically less demanding chiral ligand **1b.11** provided the bicycle **1b.12** in 90% yield and 86% *ee*. This intermediate was then advanced to the highly toxic bicyclic natural product (−)-anatoxin A (**1b.13**) in four steps.[16] The synthesis of natural products **1b.9** and **1b.13** illustrate how the transition metal-catalyzed allylic alkylation, in this case the asymmetric variant, can be used to construct structurally complex products in an inter- or intramolecular fashion through the use of various nucleophilic components.

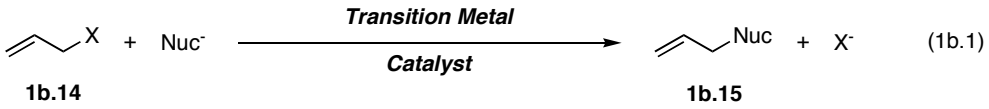
Scheme 1b.3



1.B.2 Overview

One of the key features that helps to distinguish the transition metal-catalyzed allylic alkylation from most other metal-mediated carbon-carbon bond forming reactions is the number of mechanistic possibilities there exist to yield the varied substitution products observed. Additionally, once the reaction is rendered enantioselective, the

different ways in which enantio-discrimination can be manifested invariably leads to thought provoking mechanistic analyses. The mechanistic process, in a general sense, of an allylic alkylation catalyzed by a metal species involves two components, a metal-stabilized allyl moiety and the nucleophile. However, a number of reports, particularly in the realm of nickel catalysis, have illustrated how the allylmetal intermediate can in fact act as the nucleophile in some cases. For the sake of brevity, this discussion will focus simply on those transformations in which the π-allyl intermediate acts as the electrophilic partner. An allylic substrate of type **1b.14**, where X is typically a leaving group that undergoes facile ionization in the presence of a catalyst, is often resistant to substitution under strictly anionic conditions. When treated with a nucleophile in the presence of a transition metal catalyst, the alkylation product **1b.15** is obtained.



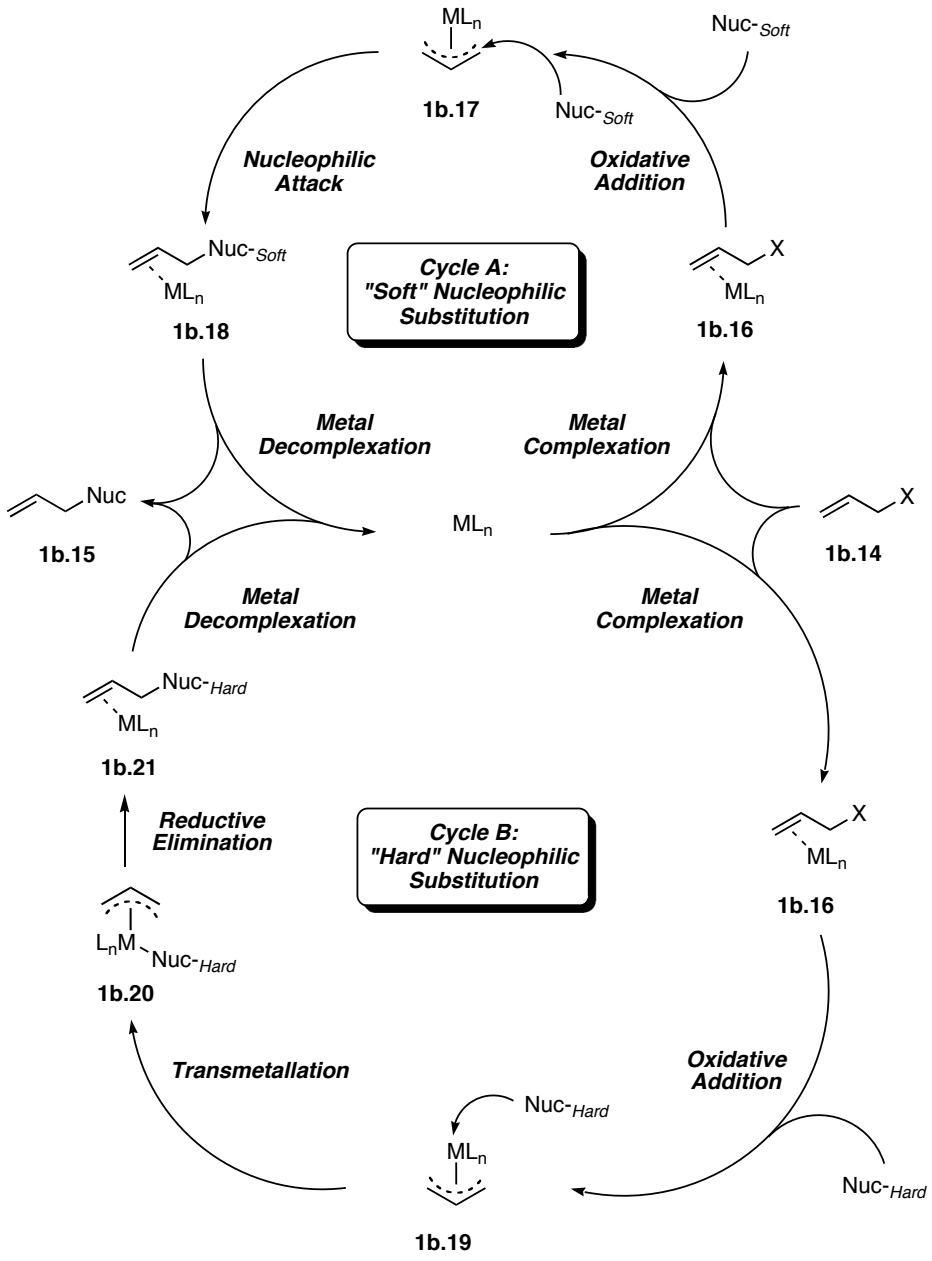
(1b.1)

The origin of group X has undergone rapid expansion in recent years to include a wide variety of leaving groups. In most cases a suitable X group can be either a halogen,[17] epoxide,[18] ester,[17] carbonate,[17,19] alcohol,[17] amine,[20] ammonium salt[21] or phosphate.[22] In general, alcohols are particularly poor leaving groups although their use has been demonstrated in limited cases. Studies performed on the allylic alkylation reaction have primarily focused on derivatives of allylic alcohols. The majority of experimental data obtained on transition metal-catalyzed processes involves the use of allylic esters, particularly acetates and carbonates.

1.B.2.1 Breadth of Nucleophiles Employed in the Transition Metal-Catalyzed Allylic Alkylation

Within the confines of the process depicted in Eq. 1b.1, the nucleophile can be considered as either "hard", characterized by a $pK_a > 25$ of the conjugate acid, or "soft", derived from a conjugate acid with a $pK_a < 15$.[23,24] Interestingly enough, whether a hard or soft nucleophile is employed dictates the mechanism through which the alkylation occurs.[13] As illustrated below in Scheme 1b.4, Cycle A shows the mechanistic pathway for the allylic alkylation of substrate **1b.14** with a "soft" nucleophile, whereas Cycle B depicts the utilization of a "hard" nucleophile. Initial complexation of the transition metal catalyst to **1b.14** provides intermediate **1b.16**, which then undergoes oxidative ionization to yield the allylmetal intermediates **1b.17** and **1b.19**. If a stabilized nucleophile is used, addition occurs in a bimolecular sense from outside the coordination sphere of the metal and ligands on the face of the allyl moiety as depicted by structure **1b.17** to provide the metal-complexed substitution product **1b.18**. Release of the catalyst completes the cycle and delivers the allylic alkylation product **1b.15**. However, if an unstabilized nucleophile is used, transmetallation occurs prior to the carbon-carbon bond-forming event. Nucleophilic attack on the metal, as depicted by structure **1b.19** provides intermediate **1b.21a.** Reductive elimination ensues yielding the metal-complexed alkylation product **1b.21**, which upon decomplexation provides the desired substitution product **1b.15**.

Scheme 1b.4



The range of nucleophiles that can be used in the transition metal-catalyzed allylic alkylation has expanded greatly over the past 20 years. Essentially, the type of anion can be divided into two classes of nucleophiles, carbon- or heteroatom-based compounds.

The carbon nucleophiles can further be dissected into the previously addressed hard and soft subclasses. Compounds that are considered to be soft nucleophiles are those of the generic formula RCXY, where R is either alkyl or H and X and Y are both functional groups that stabilize adjacent carbanions. The functional groups most often utilized include esters, ketones, nitriles, nitro groups, sulfones and sulfoxides.[7-9,17,25] Additionally, the cyclopentadienyl anion[26] and nitroalkanes[27] have also been shown to react as soft nucleophiles in metal-catalyzed allylic alkylations. The range of hard nucleophiles, although slightly more diverse, is less developed in the allylic alkylation reaction. Enolate derivatives such as tin enolates,[28-30] silyl enol ethers,[31] silyl ketene acetals[32] and copper enolates[33] are all viable coupling partners. Organometal reagents including tin,[34-36] aluminum,[37] zinc,[37,38] zirconium[37] and thallium[39] species lead to the formation of alkylation products. Grignard reagents have also been used, but they are limited in their utility due to the propensity for β-hydride elimination following transmetallation to palladium.[40] Therefore their use has been primarily restricted to methyl and phenyl Grignard, as well as others devoid of β hydrogens.

The class of heteroatom nucleophiles is much smaller than what has been observed through the use of carbon-based species. Oxygen nucleophiles[41,42] include phenols,[43,44] alcohols,[45] and carboxylates.[46] The latter typically find utility in rearrangement process in which the leaving group then acts as the nucleophile to provide an epimeric or regioisomeric allylic alcohol derivative.[47] Nitrogen nucleophiles[48-50] include simple secondary amines,[51] sulfonamides[52,53] and azides,[54] although primary amines often times suffer from the formation of diallylation byproducts. Sulfinic acids and sulfinate salts have also been shown to be useful, however sulfides have rather limited utility due to their propensity for tight coordination and subsequent poisoning of most transition metal species.[55] Reports of organometallics derived from transition

metals such as iron, nickel and cobalt[56] have appeared, and the utilization of phosphites[57] and silyl surrogate[58] nucleophiles have been examined.

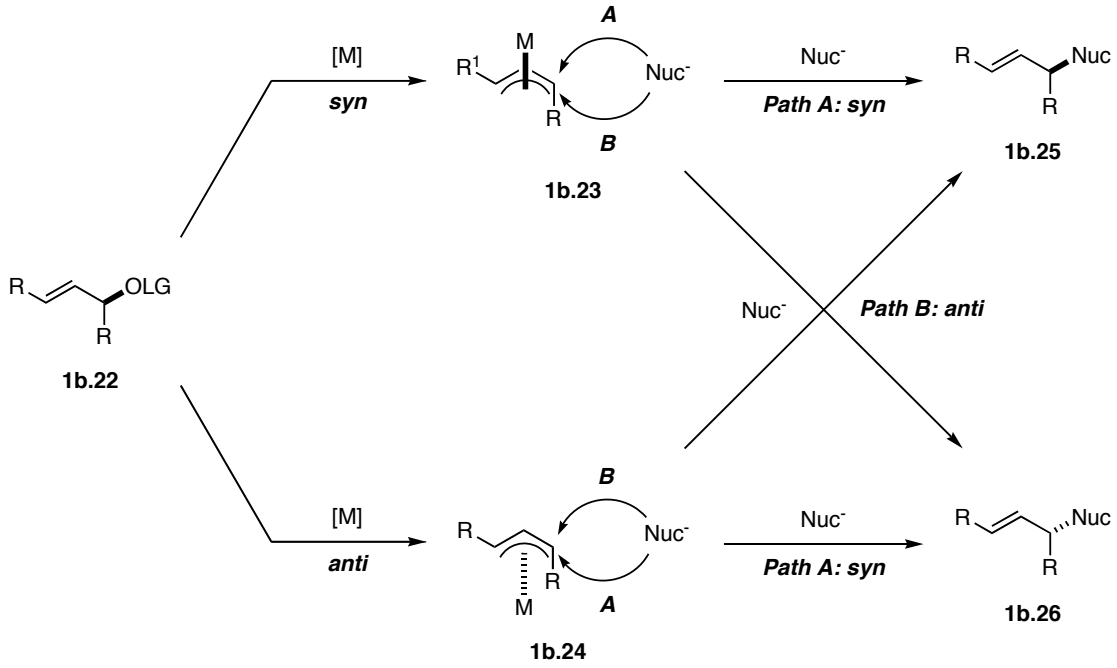
1.B.2.2 Diastereoselectivity

The allylic substitution reaction can be dissected into two major steps, the first being oxidative addition of the metal complex to the allylic substrate and secondly, nucleophilic addition to the resulting allylmetal species. In determining the diastereoselectivity of transition metal-catalyzed allylic alkylation reactions, the outcome of both of these stereochemical determining processes must be understood. Starting from an enantioenriched allylic substrate **1b.22**, the transition metal [M] can oxidatively add to the allylic system in either a *syn* or *anti* fashion to yield the diastereomeric η^3-allylmetal intermediates **1b.23** and **1b.24** (Scheme 1b.5). The nucleophile may then attack the allylmetal intermediate either on the same face (*syn* addition) as the transition metal or the opposite face (*anti* addition). *Syn* addition to complex **1b.23** provides the allylic alkylation product **1b.25**, thereby resulting in an overall retention of stereochemistry through a *syn-syn* pathway. However, *anti* addition to **1b.23** provides the epimeric substitution product **1b.26** *via* a *syn-anti* mechanism. Nucleophilic addition to intermediate **1b.24** provides the opposite product distribution. A subsequent *anti* addition yields product **1b.25** whereas the *syn* route provides **1b.26**.

The factors that dictate the stereochemical outcome of these two processes have provided the impetus for many mechanistic studies over the last few decades. The stereochemistry of the metal oxidative addition step is often dependent on the nature of the transition metal species, in conjunction with the type of leaving group and steric environment attributed to the allylic substrate. The result of nucleophilic addition is most often dictated by the basicity of the nucleophile itself. Soft nucleophiles attack in an *anti*

orientation as a result of minimizing unfavorable steric interactions between the ligands and coordination sphere of the metal and the approaching nucleophile. However, hard nucleophiles typically provide products resulting from a *syn* addition to the allylmetal intermediate *via* a reductive elimination process from the metal (except for in the case of metal enolates). The propensity for hard nucleophiles to undergo transmetallation prior to attack on the allyl ligand obviates the steric influences that dictate the path followed by stabilized anions.

Scheme 1b.5

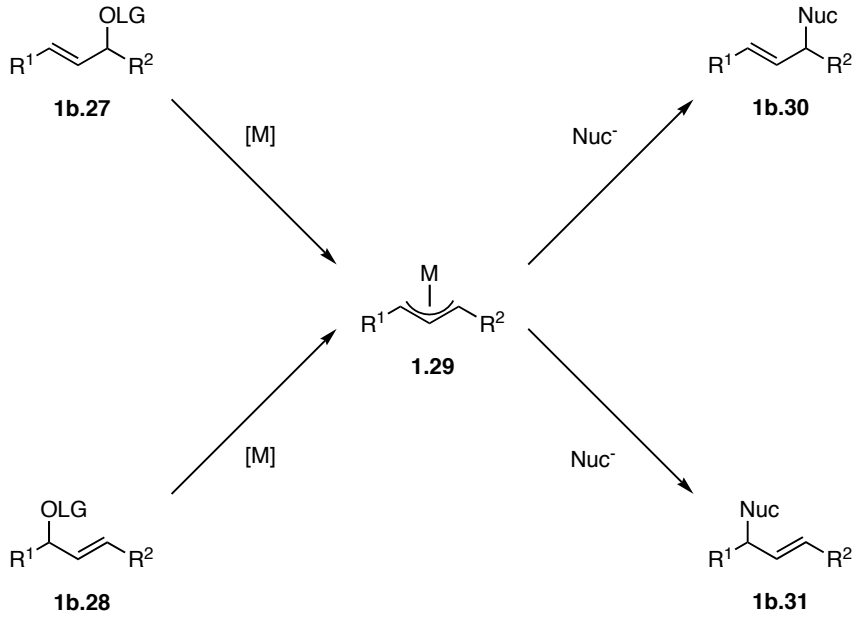


1.B.2.3 Regioselectivity

The issue of regioselectivity in transition metal-catalyzed allylic alkylations is particularly complex and will only be mentioned briefly here. The regiochemical outcome generally depends on the nature of the transition metal used, and more in-depth analysis will be reserved for the discussion sections dealing with each metal separately.

However, there are a few generalizations that may be made with regards to the anticipated regioselectivity. Under the catalysis of most transition metals, allylically transposed carbonates **1b.27** and **1b.28** will undergo ionization to yield the same π-allylmetal species **1b.29** through an $\square^1$-$\square^3$-$\square^1$ isomerization process (Scheme 1b.6). Nucleophilic addition to intermediate **1b.29** then provides the regioisomeric substitution products **1b.30** and **1b.31b.** Which product is formed preferentially depends on a delicate balance of steric and electronic factors influencing the structure of **1b.29**. These dynamics can have a profound influence in inducing asymmetry on the conformation of the π-allylmetal species *via* a distribution of electron deficiency throughout the allyl moiety. Additionally, these factors effect the ratio of regioisomers formed by distorting the position of the metal relative to the allyl moiety. The orientation of the metal is often a direct result of unfavorable steric interactions between the metal, its ligands and the substituents on the substrate. This balancing act between steric and electronic factors appears to vary with which metal complex employed and therefore will be discussed in more detail in subsequent sections of this chapter.

Scheme 1b.6



1.B.3 Palladium-Catalyzed Allylic Alkylations

The first transition metal found to exhibit catalytic activity to enable the alkylation of allylic substrates under relatively mild conditions in a regio- and stereoselective manner was palladium.[7,8,25] The use of palladium has revolutionized the area of π-allylmetal chemistry to the point in which not only has the process been established as chemo-, regio- and diastereoselective, but also significant strides have been made over the past decade to render the process asymmetric through the use of chiral palladium complexes.[13] Much of what is known about transition metal-catalyzed allylic alkylations today was elucidated from palladium-catalyzed processes. Due to the breadth of palladium-catalyzed allylic alkylations, this section will primarily focus on the substitution reaction of allylic alcohol derivatives with stabilized or "soft" nucleophiles.

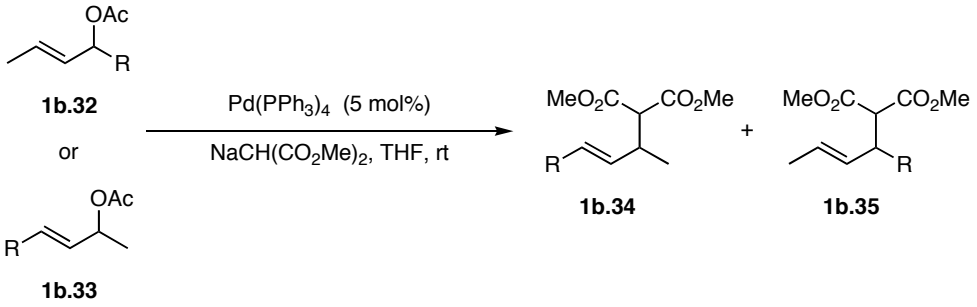
1.B.3.1 Regiochemistry

The first reports of allylic alkylations being performed in the presence of catalytic quantities of palladium species began to surface in the early 1970's. Along with the advent of π-allylpalladium species and their role in allylic alkylations, the issue of regiochemistry in the nucleophilic addition step was one of the first addressed.[8,59] In general, palladium-catalyzed processes are quite regioselective, generally providing the substitution product that arises from alkylation at the less sterically encumbered allylic terminus preferentially.[7,19,60] However, it has been reported that at lower temperatures and shorter reaction times, the reaction may proceed under kinetic control, thereby providing the product resulting from substitution at the more substituted allylic terminus.[61] Interestingly, steric factors seem to over-ride electronic influences in the distortion of π-allylpalladium intermediates.

In 1984, Keinan and Sahai published a concise look at how the steric effects from the substituents on the allylic substrate can determine the regiochemical outcome in palladium-catalyzed processes.[60] In general, when either allylic acetate **1b.32** or **1b.33** was treated with sodium dimethyl malonate in the presence of 5 mol% $Pd(PPh_3)_4$, the alkylation product **1b.34**, resulting from alkylation away from the bulky R group, was obtained preferentially (Table 1b.1). As the R group became more sterically cumbersome, the regioselectivity improved indicating that the steric environment influenced the geometric nature of the π-allylpalladium intermediate (compare entries 1 and 2). As indicated by entries 3 and 4, when the allylically transposed acetates **1b.32** and **1b.33** were subjected to the same conditions, malonate **1b.34** was obtained with >99:1 selectivity in each case indicating that both reactions proceeded through a common π-allylpalladium intermediate. Probably the most compelling result is illustrated in entry 5 wherein R was a deuterated methyl group to provide a 1:1 mixture of **1b.34** and **1b.35**.

This result indicates that in the absence of overriding steric or electronic influences, the regioisomers would be formed in equal amounts.

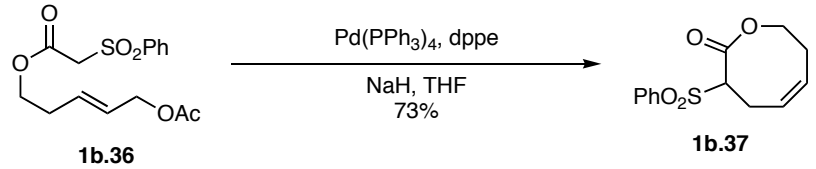
Table 1b.1. Regioselectivity in the palladium-catalyzed allylic alkylation.



Entry	*Allylic Acetate*	*R*	*Yield (%)*	*1b.34/1b.35*
1	**1b.32**	*n*-Bu	92	78:22
2	**1b.32**	*i*-Bu	90	93:7
3	**1b.32**	*i*-Pr	67	>99:1
4	**1b.33**	*i*-Pr	64	>99:1
5	**1b.32**	CD_3	84	50:50

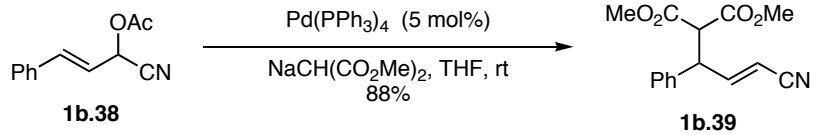
An interesting example of regiocontrol was illustrated by the discovery that when palladium was used to catalyze the allylic alkylation to synthesize medium-sized rings, the cyclized product resulting from alkylation at the least sterically congested allylic terminus was preferred over the kinetic product.[62,63] Thus intramolecular allylic alkylation of sulfonyl ester **1b.36** yielded the eight-membered ring lactone **1b.37** resulting from alkylation at the less hindered primary allylic terminus (Eq. 1b.2).[64] The fact that none of the corresponding six-membered ring regioisomer was observed is

particularly noteworthy. Although formation of the larger ring sized product corresponds to attack at the most sterically accessible allylic site, other factors including nature of the nucleophile and the ligands on palladium have been reported to contribute to the observed regioselectivity. The use of a phenyl sulfonyl ester as the nucleophile is crucial to product distribution. If the corresponding acetoacetate was employed, the six-membered lactone was formed preferentially. Additionally, if the sterically demanding ligand dppe was withheld from the reaction, mixtures of regioisomers were obtained.



1b.36 **1b.37** (1b.2)

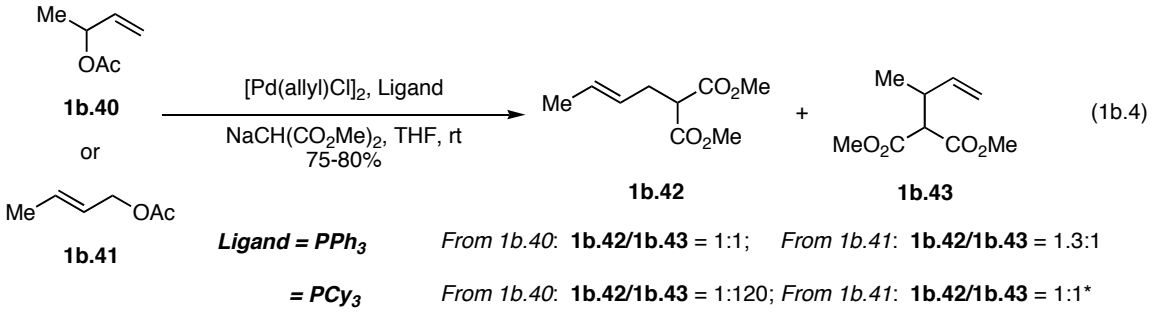
Electronic factors can also play a significant role in palladium-catalyzed allylic alkylations, although the effect is not as dramatic as that observed due to steric influences. The presence of electron-withdrawing groups on the allyl moiety have been shown to direct substitution to the proximal allylic carbon.[59] When allylic acetate **1b.38** was alkylated with sodium dimethyl malonate in the presence of $Pd(PPh_3)_4$ at room temperature, malonate **1b.39** (88%) was obtained exclusively (Eq. 1b.3). This regioselective outcome is best rationalized by extrapolating the electrophilicity of the π-allylpalladium complex to that of an allyl cation. The authors conclude from this analysis that the benzylic carbon in **1b.38** is more electron deficient thereby leading to exclusive alkylation at that site.



1b.38 **1b.39** (1b.3)

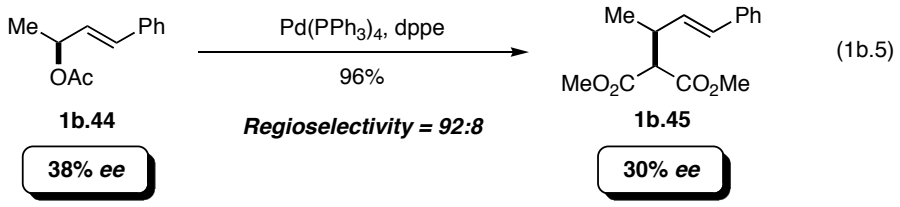
Ligand effects have also been shown to shape the regiochemical outcome of palladium-catalyzed alkylations by influencing the electronics of the π-allylpalladium species. Åkermark *et. al.* reported in 1987 a study in which they analyzed the regiocontrol in the allylic alkylation of the π-allyl complex derived from 3-methylbutene as different acceptor and donor ligands were associated with palladium.[65] The utilization of acceptor ligands on palladium had the effect of developing increased electrophilic character on the more substituted allylic terminus, thereby resulting in more of the branched regioisomer formed. Conversely, donor ligands on palladium produced a less reactive π-allylpalladium complex resulting in alkylation at the less substituted allylic terminus preferentially.

A remarkable report by Williams and coworkers in 2000 showed that the regiochemical outcome could also be affected by the steric environment the *ligand* imparts on the π-allyl intermediate.[66] The authors found that in going from PPh_3 to the bulkier PCy_3 ligand, alkylation of **1b.40** could be influenced to favor the branched alkylation product **1b.43** nearly exclusively (Eq. 1b.4). However, if allyl acetate **1b.41** was subjected to the reaction conditions, only 10% conversion was observed providing a 1:1 ratio of substitution products in low yield with PCy_3 and only limited preference for **1b.42** with PPh_3. The lack of reactivity observed with acetate **1b.41** when PCy_3 was used may be due to the inability of bulky palladium reagent to oxidatively add to an internal olefin. Likewise, the origin of regioselectivity presumably arises from the preference for the bulky catalyst, upon ionization to orient itself away from the more substituted π-allyl terminus, thus allowing for alkylation to occur at the more substituted allylic center.



1.B.3.2 Stereoselectivity

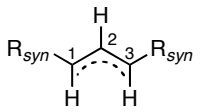
In general, palladium-catalyzed allylic alkylations proceed with overall net retention of stereochemistry as a result of an *anti-anti* mechanistic pathway. For example, alkylation of allylic acetate **1b.44** proceeded in 96% to yield the substitution product **1b.45** as a mixture (92:8) of regioisomers in 30% *ee* (Eq. 1b.5).[67] Convincing evidence for the initial *anti* addition of the palladium species to the allylic acetate was reported in 1983 by Hayashi and coworkers. They were able to isolate the π-allylpalladium species obtained from the enantioenriched allylic acetate **1b.44**. The absolute configuration of the intermediate resulted from addition of the palladium catalyst *anti* to the leaving group with minimal loss of optical purity (58% *ee* to 47% *ee*).[68]



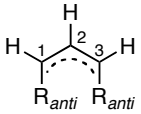
To understand many of the concepts associated with π-allyl species, it is important to understand the nomenclature assigned to substituents on the allylmetal

intermediates. Traditionally, the reference point on the allyl species is the hydrogen on the 2-carbon. Substituents are designated "*syn*" if they are aligned *syn* to the two-hydrogen, whereas those "*anti*" are likewise termed *anti*. Generally, an allyl isomer is regarded as either *syn* or *anti* in conjunction with the substituent of interest to the reaction in question.

Figure 1b.1. Nomenclature for substituents on π-allyl intermediates.



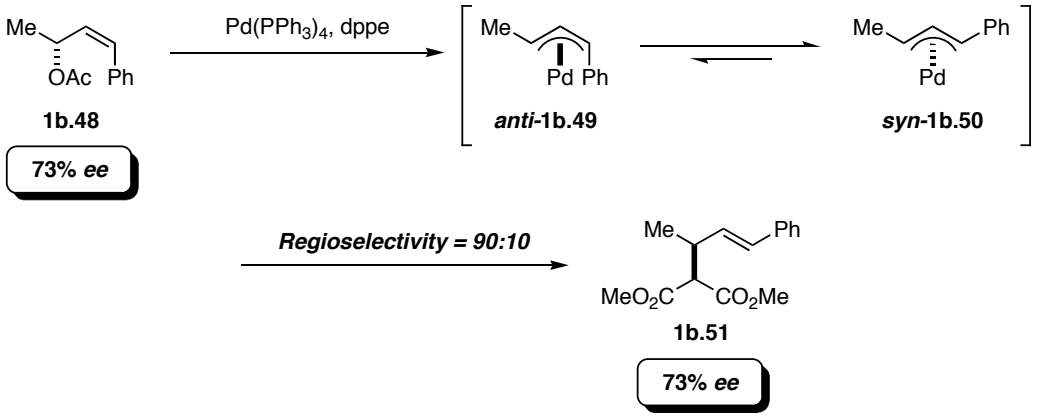
1b.46
"syn" substituents



1b.47
"anti" substituents

A particularly interesting observation is illustrated in Scheme 1b.7. When the enantioenriched *Z*-allylic acetate **1b.48** was alkylated with sodium dimethyl malonate in the presence of $Pd(PPh_3)_4$/dppe, *E*-olefinic **1b.51** was obtained with complete *inversion* of stereochemistry.[69] The formation of **1b.51** can be rationalized by the η^1-η^3-η^1 isomerization of the less stable *anti* π-allylpalladium intermediate **1b.49**, formed by oxidative addition to **1b.48**, to provide the thermodynamically more stable *syn* intermediate **1b.51.** Alkylation then occurs *via* nucleophilic attack on the face of the allyl moiety opposite the catalyst to provide the *E*-substitution product with inverted stereochemistry.

Scheme 1b.7

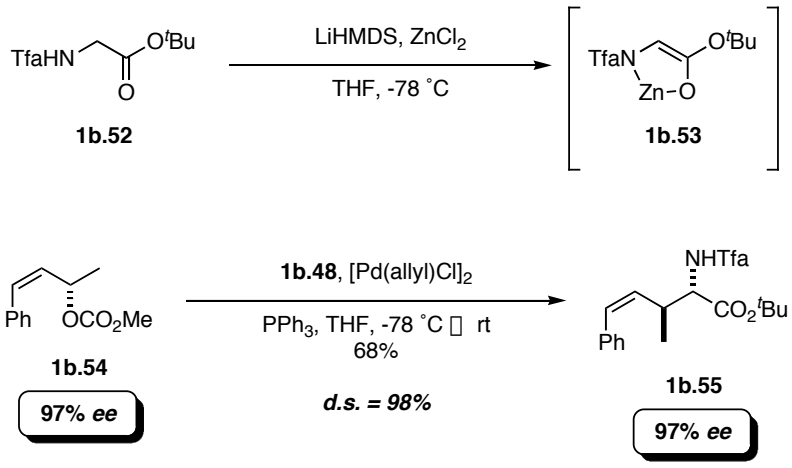


1.B.3.3 Olefin Geometry

As exemplified by the results illustrated in Scheme 1b.6, retaining the carbon-carbon double bond configuration in *Z*-allylic substrates is a substantial problem in palladium-catalyzed allylic alkylations. It has long been observed that the intermediate π-allylpalladium species isomerize to their more stable *syn* isomers at a faster rate than nucleophilic addition occurs.[70,71] However, two reports which have surfaced recently illustrate how this complication may be overcome. The first came from Kazmaier and Zumpe in 2000 as they illustrated how a more reactive nucleophile could be used to enable nucleophilic addition to occur at a faster rate than isomerization.[72] Thus, when enantioenriched allylic carbonate **1b.54** was treated with the zinc enolate **1b.53**, derived from deprotonation of **1b.52** followed by transmetallation with $ZnCl_2$, the *Z*-substitution product **1b.55** was obtained with complete chirality transfer and with excellent diastereoselectivity (98%) (Scheme 1b.8). Not only is the nature of the nucleophile key to obtaining a good *Z*/*E* ratio of the product, but also the use of a methyl carbonate leaving group was found to be critical. For example, the corresponding allylic acetate

furnished a mixture of products favoring the *E*-isomer (*E*/*Z* = 77:23) with reduced optical purity (68% *ee*) in low yield (<10%).

Scheme 1b.8



In 2002, Hayashi and coworkers reported the utility of bidentate phosphine ligands in palladium-catalyzed allylic alkylations in reducing the amount of *syn-anti* isomerization.[73] They observed that the rate of isomerization was significantly faster when bisphosphine ligands with small bite angles, the P-Pd-P angle arising from bidentate bisphosphine ligands, were employed (*i.e.* dppe = 85.8˚ vs. dppb = 94.5˚). Additionally, the electronics of the ligands significantly affected the observed outcome. Phosphine ligands that are electron-withdrawing, such as CF_3-dppf, accelerate the *syn-anti* isomerization as much as 3-4 times in comparison to neutral phosphine ligands like dppf. Phosphine ligands that are electron-donating (MeO-dppf) reduce the rate of isomerization by 4-5 fold. Therefore, *syn-anti* isomerization and hence the ratio of *Z*- and *E*-substitution products formed in palladium-catalyzed allylic substitution reactions, may be controlled through a judicial selection of bisphosphine ligands.

1.B.3.4 Summary

The use of palladium to catalyze the allylic alkylation of unsymmetrical substrates has advanced significantly over the past few decades. Most of what is understood about this important transformation has been determined by studies performed on palladium-catalyzed processes. The important aspects of the palladium-catalyzed allylic alkylation can be summarized in the following three main points. The first lesson is that the regioselectivity of the process generally provides the alkylation product arising from nucleophilic attack at the less hindered allyl terminus. Secondly, the substitution reaction proceeds with overall retention of stereochemical configuration *via* an *anti-anti* mechanism. Finally, the olefin geometry throughout the process undergoes facile isomerization to provide the energetically more stable *E*-isomer. The scope of substrate and nucleophile combinations, and the shear volume of different chemical transformations that can be enabled through the palladium-catalyzed allylic alkylation has solidified its role as a premier synthetic process.

1.B.4 Molybdenum-Catalyzed Allylic Alkylations

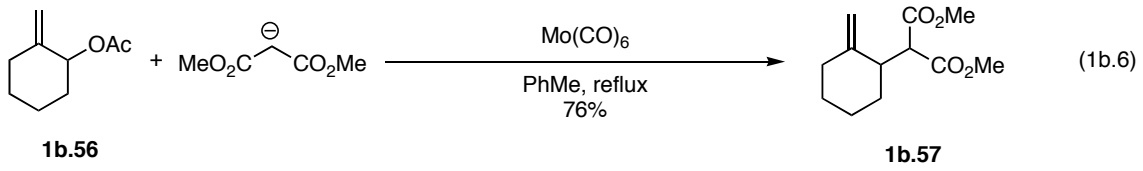
Reports of utilizing molybdenum complexes as catalysts for allylic alkylations first began to surface in the early 1980's as a result of the pioneering work performed by Trost and coworkers.[74,75] Given the success that the Trost group experienced with palladium-catalyzed allylic substitutions, a natural extension was their experimentation with other late transition metals as allylic alkylation catalysts. The focus of much of the early work was to examine how regio-, chemo- and diastereoselectivities would differ from the use of these other catalyst systems. The establishment of a molybdenum species as a viable catalyst in this class of reactions opened the door to a unique realm of possibilities untenable through traditional π-allylpalladium chemistry.

1.B.4.1 Regioselectivity

The first indication that molybdenum behaved differently as an allylic alkylation catalyst was the unusual regiochemical trend for forming the substitution products.[75,76] The regioselectivities observed in palladium-catalyzed allylic substitutions are most often attributed to steric influences that may be tuned by altering the ligand field of the metal. However, initial observations in molybdenum-catalyzed alkylations indicated that steric and electronic factors could at times be working in opposing directions.[77-81] If a suitable balance was not attained, the ratio of regioisomers could be fairly poor. However, if the right set of reaction conditions were found, either regioisomer could be prepared selectively. Limited success was encountered in discriminating primary and tertiary allylic termini by altering the nature of the nucleophile under palladium-catalyzed conditions.[82] Attempts to direct alkylation by changing the nature of the catalyst enhanced substitution at the primary center, but typically failed in directing alkylation at the tertiary carbon. In initial studies, the more electropositive octahedral molybdenum complexes were thought to be ideal candidates to enhance electronic influences in the intermediate η^3-allylmetal species such that they would override steric preferences to provide alkylation at the more substituted allylic termini more.[83] [77]

Catalysts derived from $Mo(CO)_6$ were examined first.[74] Initial studies indicated that the molybdenum-bipyridyl complex, $Mo(CO)_4$bipy proved advantageous. However, upon further analysis this catalyst was determined not to be sufficiently reactive with a wide range of substrates, and at times gave inconsistent regioselectivities. $Mo(CO)_6$ itself was found to be reactive enough to alkylate allyl acetate **1b.56** with the anion of dimethyl malonate to give **1b.57** in 76% yield as one regioisomer (Eq. 1b.6).[77] To examine the effect of η^3-ketoester substitution on regioselectivity, treatment of **1b.56** with the sodium

anion of methyl 5-methyl-3-oxohexanoate also provided the analogous regioisomer in 91% yield.[77]

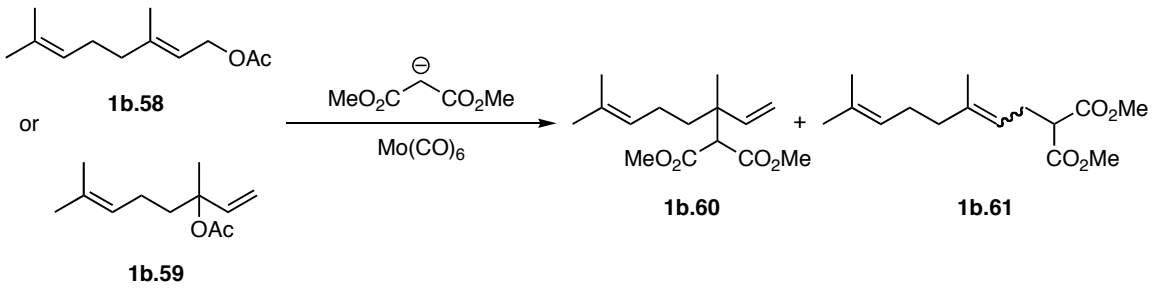


1b.56 **1b.57** (1b.6)

The sodium anion of dimethyl malonate was able to discriminate between primary and secondary allylic termini with good selectivity, but would the regiochemical trends hold when the nucleophile was asked to differentiate between a tertiary and primary allylic carbon? To answer this question, acetates **1b.58** and **1b.59** acetate were treated with sodium dimethyl malonate in the presence of $Mo(CO)_6$ to yield mixtures of the branched substitution product **1b.60** and both *E*- and *Z*-isomers of the corresponding linear product **1b.61** in good yield (Table 1b.2).[83] In each case, the major product obtained was **1b.60** resulting from alkylation at the tertiary allylic carbon. Although alkylation of either **1b.58** or **1b.59** provided the same major product, the rate at which substitution occurred was markedly different. Allylic acetate **1b.58** containing a trisubstituted olefin underwent alkylation at a significantly slower rate than did the corresponding monosubstituted terminal alkene. This result suggests that oxidative addition of the molybdenum catalyst may be sensitive to the steric environment of the allylic system such that more congested substrates result in slower formation of the π-allyl species (entries 1 and 2 versus entry 4). Alternatively, the reason could be that the ionization of **1b.54** occurs at a faster rate due to the ability of low valent metals to coordinate monosubstituted olefins easier than the corresponding disubstituted carbon-carbon double bonds. Intramolecular displacement through the aid of a non-bonding pair

of electrons allows for steric hindrance at the tertiary site to be minimized, and the weaker C-O bond of the more substituted acetate to undergo ionization at a faster rate. The nature of the base also had an effect on the rate and regioselectivity of the alkylation.[83] When a coordinating base such as *N,O*-bis(trimethylsilyl)acetamide was used, the regioselectivity improved dramatically (entry 3). However, if the base was too strongly coordinating, the reaction was shutdown presumably due to poisoning of the catalyst (entry 5).

Table 1b.2. Regioselectivity in the molybedenum-catalyzed allylic alkylation.



Entry	*Substrate*	*Base*	*Time (h)*	*Yield (%)*	*1b.60/E-1b.61/Z-1b.61*
1	**1b.59**	NaH	3	80	85:12:3
2	**1b.59**	KH	2	82	80:17:3
3	**1b.59**	BSA	1.5	82	97:1.5:1.5
4	**1b.58**	NaH	48	65	85:12:3
5	**1b.59**	DBU	48	N.R.	□

In analyzing the regiochemical outcome of the molybdenum-catalyzed allylic alkylation, a number of different factors must be considered. Inherently, the

regiochemistry of the reaction relies more on electronic than steric factors. Often times this leads to substitution at the more substituted allylic site where there exists the lowest electron density within the allylic system. However, when bulky nucleophiles are used, this trend can be reversed to provide the corresponding linear substitution products. One of the more attractive aspects in the molybdenum-catalyzed allylic alkylation is the inherent ability of the metal species to seemingly override existing factors within the substrate to consistently yield products resulting from primarily electronic control.

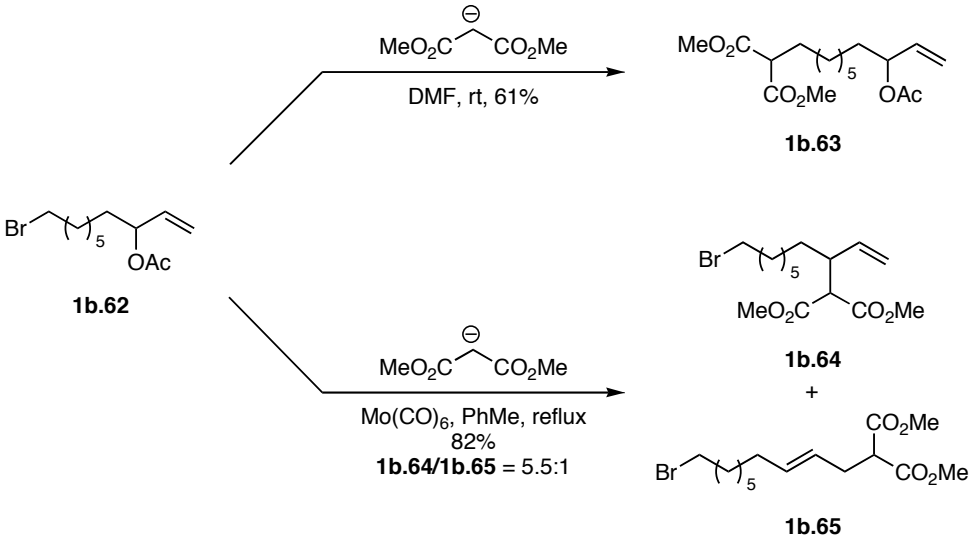
The use of protecting groups to mask functionality within a substrate such that other entities present can be manipulated has become a mainstay in the synthesis of natural products. Unfortunately, the employment of protecting groups often adds unwanted synthetic operations to a route, and typically suffers from poor atom economy by generating waste. Therefore, if chemical transformations could be performed *chemoselectively* in the presence of other reactive functionality, without resorting to the use of protecting groups, there could be a significant advantage in synthetic efficiency provided the route itself was optimal.

In 1987, Trost and coworkers examined whether molybdenum-catalyzed allylic alkylations could be performed on substrates containing other leaving groups that were subject to nucleophilic displacement.[75] Under standard, non-transition metal-catalyzed displacement conditions, nucleophiles, such as malonate anions, will react with primary alkyl halides to provide the corresponding substitution products. The question was thus: would molybdenum-catalyzed allylic alkylations proceed faster than simple alkylations.

As illustrated in Scheme 1b.9, the chemoselectivity of the $Mo(CO)_6$-catalyzed allylic alkylation was analyzed by utilizing acetate **1b.62** containing competing functionality.[75] Treatment of alkyl bromide **1b.62** with sodium dimethyl malonate in the absence of a molybdenum catalyst provided solely malonate **1b.63** in 61% yield (Scheme

1b.8). However, when the same reaction was run in the presence of $Mo(CO)_6$, a mixture (5.5:1) of regioisomers **1b.64/1b.65** was obtained in excellent yield. Of particular note is the fact that the alkyl bromide functionality remained intact to allow for further manipulation at a later stage.

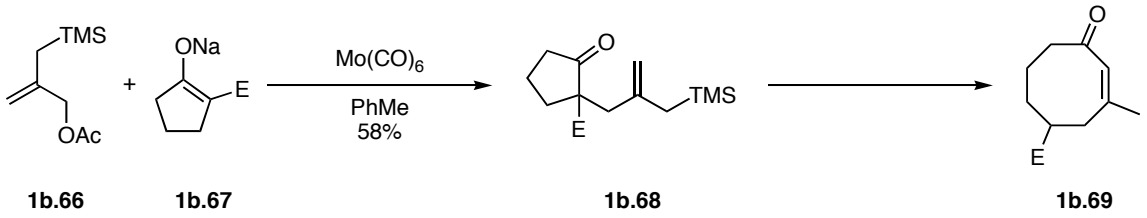
Scheme 1b.9



It has been well established that allylsilanes undergo protodesilylation in palladium catalyzed processes.[84,85] Given the reactivity and synthetic utility of allylsilanes, it would be desirable to enable the metal-catalyzed allylic alkylation of an allyl acetate with a stabilized nucleophile while not affecting a pendant allylsilane functionality. It is therefore noteworthy that treatment of allyl acetate **1b.66** with $Mo(CO)_6$ and the sodium enolate **1b.67** provided the allylic alkylation product **1b.68** in 58% yield without evidence of protodesilylation (Scheme 1b.9).[75] One may attribute the lack of C-Si bond cleavage in the molybdenum-catalyzed case to the fact that π-allylpalladium intermediates are more electrophilic than the corresponding π-allylmolybdenum species. The synthetic utility of intermediates such as **1b.68** was

further illustrated by the intramolecular alkylation/ring expansion to yield cyclooctenone **1b.69** en route to muscone.[86]

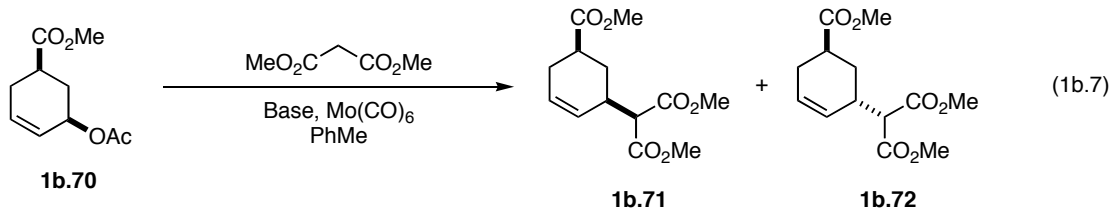
Scheme 1b.10



1b.66 **1b.67** **1b.68** **1b.69**

1.B.4.2 Stereoselectivity

The issue of diastereoselectivity in molybdenum-catalyzed allylic alkylations was first investigated using the allyl acetate **1b.70** (Eq. 1b.7).[75] The diastereoselectivity of the reaction showed a remarkable dependence on the base used, and, not as surprisingly, the nature of the nucleophile. Treatment of **1b.70** with sodium dimethyl malonate in the presence of $Mo(CO)_6$ produced *syn* and *anti* diastereomers **1b.71** and **1b.72** in equal amounts. When BSA was used as the base however, only **1b.66** was formed (75%). Thus, the reaction proceeded cleanly with overall retention of configuration as observed in palladium-catalyzed reactions.

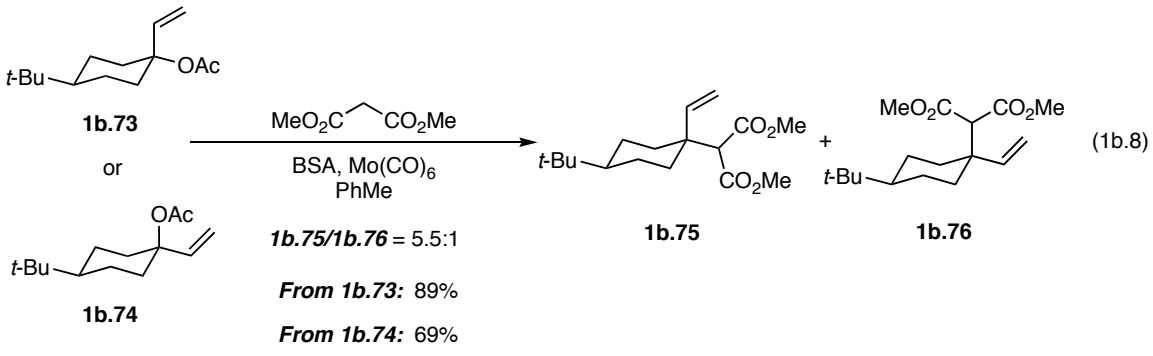


1b.70 **1b.71** **1b.72** (1b.7)

NaH:	90%	50	50
BSA:	75%	100	0

Although the alkylation of allyl acetate **1b.70** with sodiodimethyl malonate was not stereoselective, the reaction of sodiodimethyl methylmalonate with **1b.70** provided a mixture (8:1) of *syn* and *anti* diastereomers **1b.71** and **1b.72** respectively.[75] In this case the diastereoselectivity improved when a more sterically hindered nucleophile was used, illustrating that the allylic alkylation could still be diastereoselective in the presence of $Mo(CO)_6$ with sodium hydride as the base. In 1990 Trost and Merlic reported the use of the *tert*-butylisonitrile molybdenum complex, $Mo(CO)_2(CNC_4H_9\text{-}t)_4$, and showed that the stereorandom reaction of **1b.70** with sodiodimethyl malonate as illustrated in Eq. 1b.7 proceeded with excellent stereocontrol in the presence of the isonitrile complex (dr > 99:1, 70% yield).[79] This report showed that the reaction could proceed diastereoselectively with simple sodium salts of malonate nucleophiles with the right ligands on molybdenum.

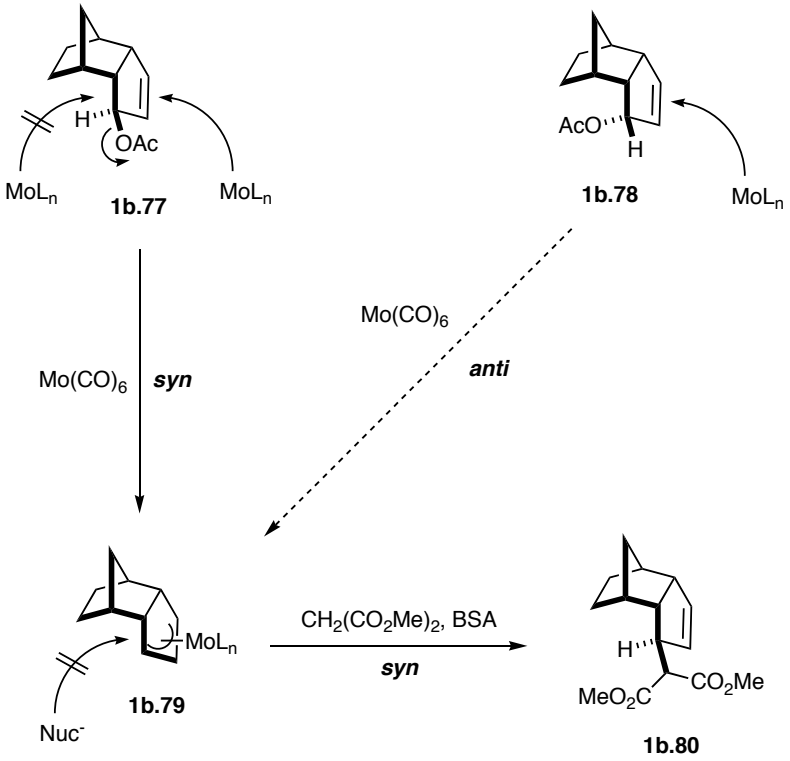
Acyclic allylic acetates have also been used as substrates. Equatorial allylic acetate **1b.73** and its axial stereoisomer **1b.74** were both treated with dimethyl malonate and BSA in the presence of $Mo(CO)_6$ to determine how the diastereoselectivity of the reaction would be affected when proceeding through a sterically biased acyclic □-allylmolybdenum intermediate (Eq. 1b.8).[75,77] Thus, treatment of either **1b.73** or **1b.74** yielded a mixture (5.5:1) of diastereomers **1b.75** and **1b.76** favoring equatorial attack.



(1b.8)

The stereochemical outcome in molybdenum catalyzed allylic alkylations has been a subject of debate since 1995 when the first suggestions of the involvement of an unprecedented *syn-syn* mechanism began to surface. Given the net retention of stereochemistry observed in the absence of factors inherent to the substrate, the molybdenum-catalyzed reaction was originally believed to proceed through an *anti-anti* mechanism similar to the palladium catalyzed reaction.[74,77,83] However, encouraged by the observations of Faller[87] and Liebeskind[88] that showed stoichiometric reactions produced molybdenum η^3-complexes through a *syn* pathway, Kocovsky examined the $Mo(CO)_6$-catalyzed alkylation of bicycle **1b.77** (Scheme 1b.11).[89] Allyl acetate **1b.77** is inert to Pd(0)-catalyzed substitutions, but its epimer **1b.78** undergoes alkylation with PhZnCl in the presence of a palladium(0) species, presumably through an *anti-syn* pathway. On the other hand, allylic acetate **1b.78** was unreactive to the lithium salt of dimethyl malonate under palladium-catalyzed conditions, which should proceed *via* an *anti-anti* process. These observations are rationalized by the hypothesis in that for allyl acetate **1b.77**, the *endo* face of the bicyclic ring system is too sterically congested to allow for metal complexation followed by ionization with palladium. However, the epimer **1b.78** can react to form the η^3-allylpalladium intermediate **1b.79** from the *exo* face. The resulting η^3-allylmetal complex can only react with unstabilized nucleophiles that add in a *syn* fashion *via* transmetallation followed by reductive elimination, and not stabilized malonates which attack from the opposite face that the metal rests on, in the case of **1b.79** the more sterically congested endo approach.

Scheme 1b.11

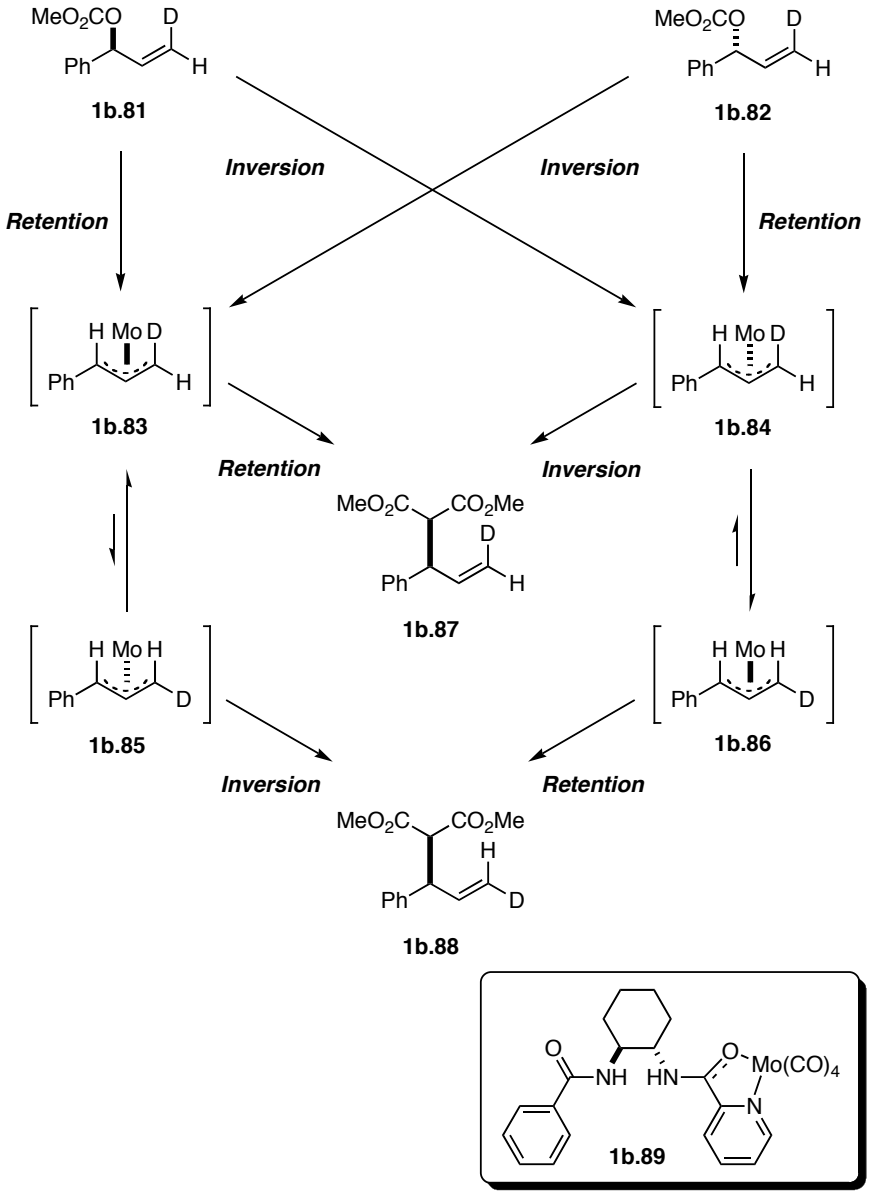


When Kocovsky and coworkers treated allyl acetate **1b.77** with $Mo(CO)_6$, dimethyl malonate and BSA, the alkylation product **1b.80** was produced in >90% conversion. Under identical conditions, the epimeric acetate **1b.78** was inert, providing none of the desired product. These results seem to suggest that a *syn-syn* mechanism is in effect under molybdenum-catalyzed allylic alkylation conditions. Additionally, the authors speculated that the rate of the reaction was enhanced by coordination of the molybdenum center to the carbonyl oxygen of the acetate to facilitate delivery of the catalyst and act as a Lewis acid in the ionization step. This hypothesis was examined by alkylation of the corresponding allylic trifluoroacetates, because their electron-withdrawing capability would presumably favor the *anti* mechanism. The corresponding carbamates were also examined due to their electron-donating influence that would

presumably facilitate precoordination of the metal, thereby causing a rate enhancement in the *syn* mechanism. In accordance with the hypothesis, the trifluoroacetate derived from **1b.77** reacted approximately three times slower than the corresponding allyl acetate, and the carbamate benefited from a substantial rate increase.[89] Conversely, the trifluoroacetate derived from **1b.78** reacted much faster than the acetate whereas the corresponding carbamate was essentially inert to the reaction conditions. These additional observations lent support to the hypothesis that molybdenum-catalyzed allylic alkylations operate under a *syn-syn* mechanistic pathway.

Finally in 2003 there appeared conclusive evidence for molybdenum-catalyzed allylic alkylations operating under a *syn-syn* mechanism. Lloyd-Jones and coworkers reported that they were able to crystallize the intermediate π-allylmolybdenum complexes from the enantiomeric allylic carbonates **1b.81** and **1b.82** in the presence of chiral ligand **1b.89**. When this complex was treated with a malonate nucleophile the substitution products resulting from an overall *syn-syn* addition were obtained (Scheme 1b.12).[90] Thus, treatment of allylic carbonate **1b.81** with the chiral molybdenum catalyst **1b.89** cleanly provided the π-allyl complex **1b.83** whose ^{1}H NMR data corresponded with the corresponding protio complex. Addition of malonate nucleophile to intermediate **1b.83** provided malonate **1b.87** with net retention and no deuteron transposition, presumably *via* a *syn* addition pathway. When carbonate **1b.82** was treated with **1b.89**, the ^{1}H NMR data obtained corresponded to deuteroisomer **1b.86**, which was formed by an π^3-π^1-π^3 isomerization of the unobserved metal-stabilized intermediate **1b.84**. Subsequent treatment with sodiodimethyl malonate provided the retention product **1b.88** with no deuteron transposition. These results seem to provide conclusive evidence for a *syn-syn* mechanistic pathway in the molybdenum-catalyzed allylic alkylation.

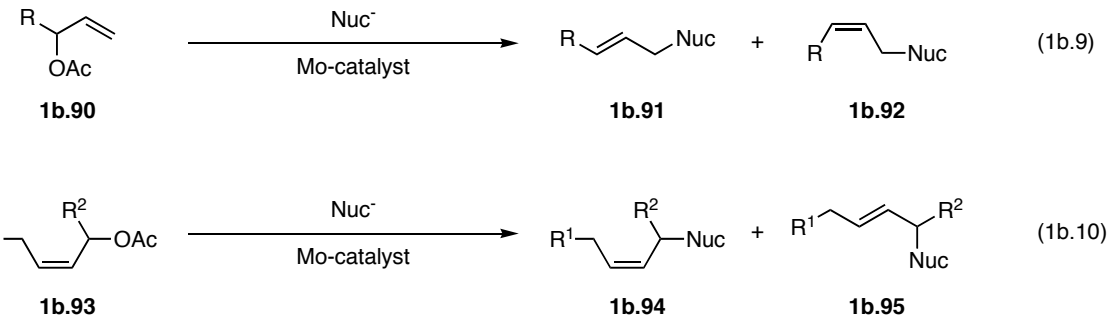
Scheme 1b.12



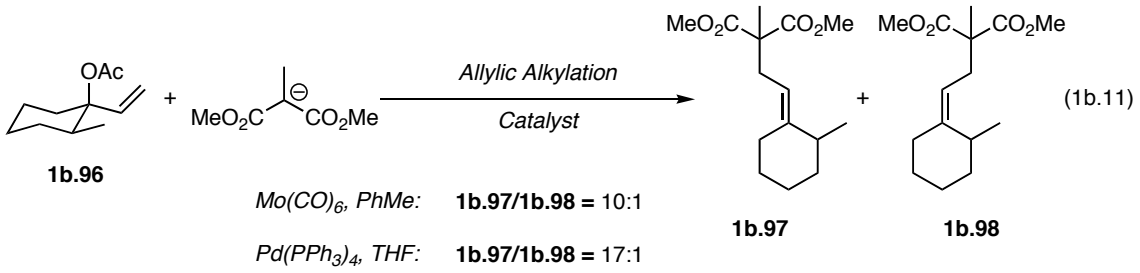
1.B.4.3 Geometric Selectivity

The issue of olefin geometry in molybdenum-catalyzed allylic substitution was addressed in two ways. The first, as illustrated in Eq. 1b.9, involves the alkylation of a secondary allyl acetate with a terminal olefin as **1b.90** to yield one of two geometric

isomers **1b.91** and **1b.92** by alkylation at the primary allylic terminus. The most common manifestation of this type is observed by the substitution of a tertiary allylic acetate at the terminal olefin to yield the corresponding *Z*- and *E*-isomers of a trisubstituted carbon-carbon double bond. The second involves the retention or isomerization of olefin geometry during the course of the reaction, as explored in the context of palladium-catalyzed alkylations. The most common example involves starting from a *Z*-allyl acetate **1b.93** that can lead to either the *Z*- or *E*-alkylation products **1b.94** and **1b.95** respectively (Eq. 1b.10).

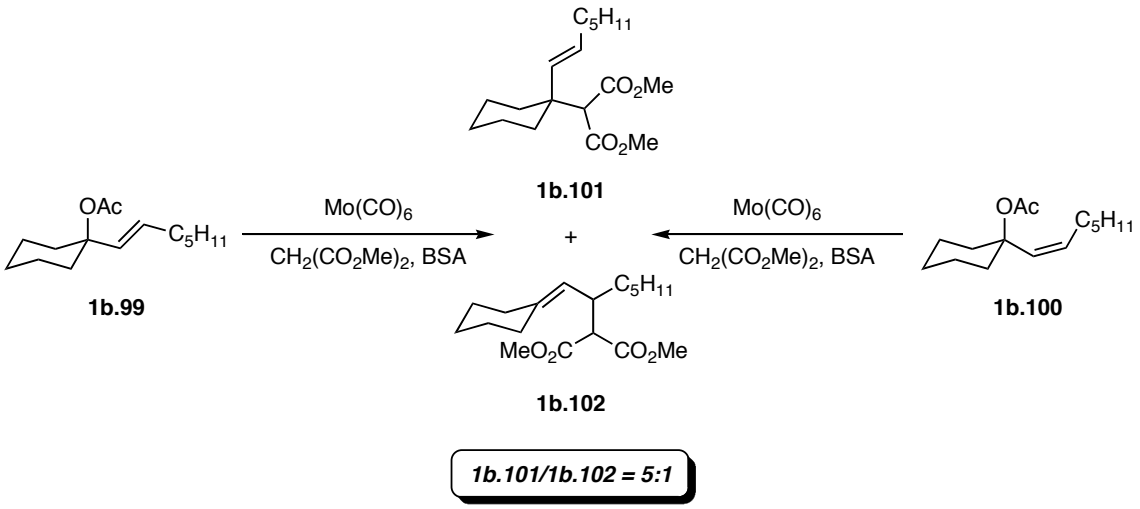


The first analysis of olefin geometry in the molybdenum-catalyzed allylic alkylation was performed by examining the reaction of the exocyclic allylic acetate **1b.96** with sodium dimethyl methylmalonate in the presence of $Mo(CO)_6$ in PhMe to provide a mixture (10:1) of **1b.97** and **1b.98** respectively, favoring the *E*-substitution product (Eq. 1b.11).[75] In comparison, palladium-catalyzed allylic alkylation of **1b.96** provided a similar mixture with the *E*-alkylation product **1b.97** being formed with somewhat higher selectivity.



In order to examine the extent to which olefin geometry is retained, the *E*- and *Z*-exocyclic allyl acetates **1b.99** and **1b.100** were alkylated with dimethyl malonate and BSA in the presence of $Mo(CO)_6$ (Scheme 1b.13).[75] The alkylation of both substrates proceeded in good yield to provide the same mixture (5:1) of products **1b.101** and **1b.101c.** Whether acetate **1b.99** or **1b.100** was used, the *E*-olefin was the only carbon-carbon double bond isomer observed. The authors provide this result as evidence that there existed an equilibrium of the molybdenum-stabilized π-allyl intermediates and that alkylation occurred at a slower rate than equilibration.

Scheme 1b.13



1.B.4.4 Summary

In general, the molybdenum-catalyzed allylic alkylations proceed with comparable or better selectivity than what is observed with most transition metals capable of catalyzing the allylic substitution reaction. The chemoselectivity of the transformation is often superior and the *E*-olefin selectivity observed is nearly as good as the analogous palladium-catalyzed processes. The stereoselectivity for diastereomerically pure substrates is on par with the trends associated with other transition metal catalysts. When enantiomerically enriched allylic substrates are alkylated under molybdenum-catalyzed conditions, enantiopurity is maintained, and the reaction has been found to proceed through a supposedly unique *syn-syn*. Additionally, the regiochemical trends are reversed from those observed with palladium. In general, alkylation at the more substituted allylic terminus proceeded preferentially. There are, however, some drawbacks to its use. These include the poisoning of the molybdenum catalyst by strongly Lewis basic reaction conditions (*i.e.* the use of DBU as a base shut down the reaction completely)[83] and the relatively low catalytic turnover numbers in comparison to palladium. However, the increased air-stability and low cost of molybdenum negates some of the drawbacks associated with its use. One primary advantage in choosing a molybdenum catalyst to perform an allylic alkylation is that the regiochemical trends provide an opportunity to construct tertiary and quaternary centers, thereby lending itself applicable toward asymmetric catalysis through the use of chiral ligands as depicted in section 1b.0 and will be discussed further.

1.B.5 Iridium-Catalyzed Allylic Alkylations

Over the past six years Takeuchi and coworkers have pioneered the use of iridium-based catalysts to achieve allylic alkylations.[91] When initial reports on the use of

iridium catalysts began to surface, a number of different transition metals had already been found to catalyze this reaction. The majority of work done on the development of iridium catalysis has centered around their utility as exquisite hydrogenation[92-94] and hydrosilylation[95] catalysts, and there had been a lack of key carbon-carbon bond forming operations. The use of iridium species to form carbon-carbon bonds stereoselectively for the construction of complex intermediates was a relatively unexplored area until the late 1990's.[96,97] However, Takeuchi has shown that iridium catalysis contributed to the expanding the field of allylic alkylation catalysts.

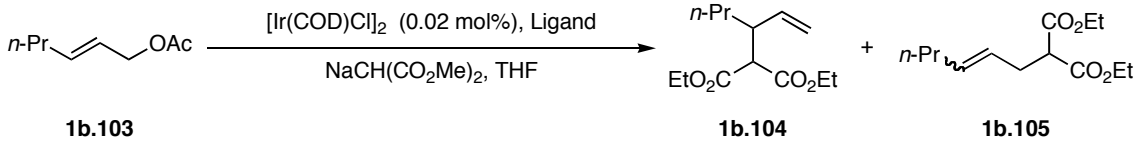
1.B.5.1 Regioselectivity

The control of regiochemistry in transition metal-catalyzed allylic alkylations is arguably the most important factor in determining the utility of a particular catalyst. As already mentioned, palladium typically results in alkylation at the least substituted allylic terminus, whereas molybdenum species selectively provide the branched regioisomers. However, prior to 1997, the catalysts that preferentially provided branched products did so using only a limited variety of substrates. Molybdenum[83]-, tungsten[98]- and ruthenium[99]-catalyzed processes provided the products arising from substitution at the more substituted terminus, but only on aryl or simple substituted substrates. However, Takeuchi and coworkers discovered and developed iridium complexes that not only catalyzed the allylic alkylation reaction, but did so regioselectively to yield the branched regioisomer.[91]

Preliminary studies illustrated that as little as 4 mol% of the iridium complex, $[Ir(COD)Cl]_2$ was capable of catalyzing the allylic alkylation of **1b.103** with sodium diethyl malonate in a modest 66% yield after 19 h of heating under reflux (Table 1b.3, entry 1).[100-102] Interestingly, the regioselectivity favored the linear substitution product

1b.105.[101] The use of phosphine ligands allowed the reaction to be run under more mild conditions while having a significant effect on the yield of the reaction, and also the regioselectivity.[100,101] For example, one equivalent of triphenylphosphite to iridium catalyst increased the yield to 90% and reversed the regioselectivity to favor the branched isomer **1b.104** (regioselectivity = 96:4) (entry 2). Use of either $P(O\text{-}p\text{-}MeC_6H_4)_3$ or $P(O\text{-}p\text{-}FC_6H_4)_3$ as ligands slowed the reactions but did not increase the yield or show a dramatic effect on the regioselectivity (entries 3 and 4). The addition of triethylphosphite provided the products **1b.104** and **1b.105** in good yield, but poor regioselectivity, requiring reflux temperatures to see any conversion to product (entry 5). A reaction run in the presence of triphenylphosphine and dppe proceeded in poor yields resulting in a reversal of regioselectivity to favor **1b.105** (entries 6 and 7). In general, $P(OPh)_3$ was found to provide superior results and was used as the additive in subsequent studies.

Table 1b.3. Selectivity in the iridium-catalyzed allylic alkylation of **1b.103**.

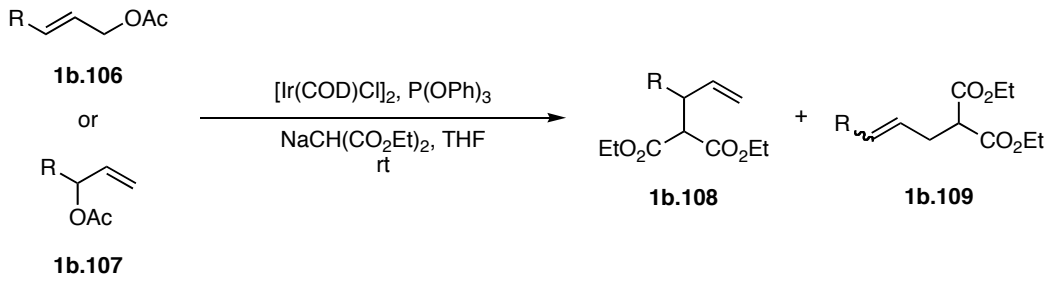


1b.103 **1b.104** **1b.105**

Entry	*Ligand*	*Temperature*	*Time (h)*	*Yield (%)*	*1b.104/1b.105*	*E/Z*
1		reflux	19	66	12:88	97:3
2	$P(OPh)_3$	rt	3	90	96:4	78:22
3	$P(O\text{-}p\text{-}MeC_6H_4)_3$	rt	8	81	95:5	73:27
4	$P(O\text{-}p\text{-}FC_6H_4)_3$	rt	23	55	94:6	94:6
5	$P(OEt)_3$	reflux	3	81	59:41	90:10
6	PPh_3	reflux	16	6	24:76	63:37
7	dppe	reflux	16	18	39:61	94:6

The scope of the reaction was next examined by analyzing the behavior of allylically transposed acetates **1b.106** and **1b.107** under the optimized combination of ligand and iridium complex for the desired transformation (Table 1b.4). As in other experiments, alkylation of the linear allylic acetate **1b.106** provided the branched product **1b.108** in excellent yields (≥77%) and regioselectivities (≥95:5) regardless of whether the R group was phenyl (entry 3), methyl (entry 1) or a long alkyl chain (entry 5).[100] Likewise, the secondary allylic acetate **1b.102** proceeded regioselectively (≥95:5) to provide the branched substitution product in excellent yields (≥86%) regardless of the nature of the R group (entries 2, 4 and 6).

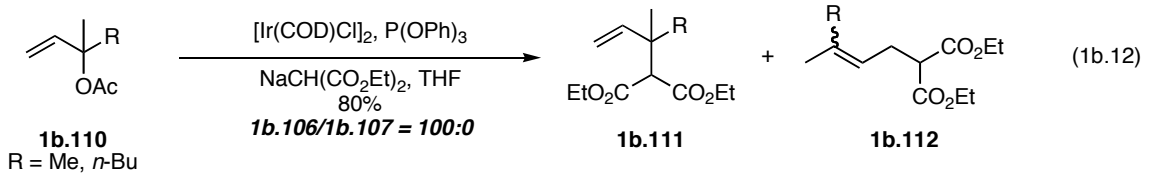
Table 1b.4. Selectivity in the iridium-catalyzed allylic alkylation of **1b.106** and **1b.107**.



Entry	*Substrate*	*R*	*Yield (%)*	*1b.108/1b.109*	*E/Z*
1	**1b.106**	Me	77	97:3	-
2	**1b.107**	*n*-Pr	86	95:5	78:22
3	**1b.106**	Ph	98	99:1	100:0
4	**1b.107**	Ph	91	99:1	79:21
5	**1b.106**	Oct	95	95:5	69:31
6	**1b.107**	Oct	95	95:5	78:22

To examine the scope of the substitution pattern tolerated in iridium-catalyzed allylic alkylation reactions, the tertiary allylic acetate **1b.110** and the primary allylic acetate **1b.1113** were examined under optimized conditions.[100] The reaction illustrated in Eq. 1b.12 proceeded in good yield and with complete regioselectivity to yield the substitution product **1b.111** (R = Me, *n*-Bu) bearing a quaternary carbon center. Conversely, attempted alkylation of the primary allylic acetate **1b.113** failed, yielding neither of the regioisomeric substitution products **1b.114** or **1b.115** (Eq. 1b.13). This result is not altogether surprising because most other transition metal catalysts failed to

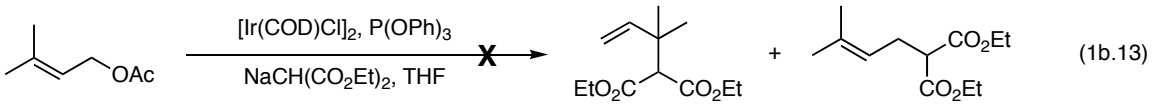
promote the alkylation of substrates similar in substitution to acetate **1b.113**. It is thought that the lack of reactivity is due to the inability of the metal catalyst to efficiently oxidatively ionize the allylic substrate in an S_N2' fashion due to the increased steric interference caused by the trisubstituted olefin.



1b.110
R = Me, *n*-Bu

1b.111 **1b.112**

(1b.12)



1b.113

1b.114 **1b.115**

(1b.13)

1.B.5.2 Olefin Geometry

Although the regioselective trends observed make iridium a synthetically attractive catalyst, one of its more intriguing properties is that in a few cases the olefin geometry was retained regardless of the structure of the starting allylic substrate.[100,101] The unique nature of the iridium catalytic system is evident by comparison with other catalysts. For example, the use of both palladium[7] and molybdenum[75] catalysts, lead to rapid isomerization of *Z*-allylic substrates to the corresponding *E*-substitution products. It has been postulated that in the allylic alkylations catalyzed by these transition metals, nucleophilic addition was believed to proceed at a slower rate than η^3-η^1-η^3 isomerization.[73] Upon isomerization, the more stable *anti* allylmetal species should predominate, and alkylation would then occur to provide the corresponding *trans*-substitution product. Apparently in the iridium-catalyzed process, as illustrated by the

results obtained from the alkylation of *Z*-allylic acetate **1b.116**, the rate of nucleophilic attack is faster than isomerization.[101]

For example the iridium-catalyzed allylic alkylation of the *Z*-allylic acetate **1b.116** with a series of ligands was examined (Table 1b.5).[100] Use of $P(OPh)_3$ as the phosphine additive provided the alkylation product **1b.117** in a 93:7 *Z*/*E* ratio, but with poor regioselectivity (**1b.117**/**1b.118** = 75:25) (entry 1). However, when the bulkier phosphite ligand, $P(O\text{-}2\text{-}t\text{-}Bu\text{-}4\text{-}MeC_6H_3)_3$ was used, the reaction proceeded in good yields to give synthetically useful *Z*/*E* ratios of substitution products. The reaction also provided the malonate **1b.117** in impressive linear/branched regioselectivities (≥ 97:3) regardless of the substituent R (entries 2-4). The only potential drawback to these conditions is the need to achieve refluxing temperatures to enable the alkylation to proceed in a synthetically useful time frame.

Table 1b.5. *Z*-Selectivity in the iridium-catalyze allylic alkylation of **1b.116**.

1b.116 **1b.117** **1b.118**

Entry	*R*	*Ligand*	*Yield (%)*	*1b.117*/*1b.118*	*Z*/*E*
1	*n*-Pr[a]	$P(OPh)_3$	81	75:25	93:7
2	*n*-Pr[b]	$P(O\text{-}2\text{-}t\text{-}Bu\text{-}4\text{-}MeC_6H_3)_3$	85	97:3	92:8
3	*n*-Hex[b]	$P(O\text{-}2\text{-}t\text{-}Bu\text{-}4\text{-}MeC_6H_3)_3$	86	98:2	90:10
4	*n*-Oct[b]	$P(O\text{-}2\text{-}t\text{-}Bu\text{-}4\text{-}MeC_6H_3)_3$	84	98:2	88:12

[a]Reaction reached completion in 2 h at room temperature. [b]Reaction reached completion in 3-5 h at reflux.

1.B.5.3 Summary

In conclusion, the iridium-catalyzed allylic alkylation, although not fully developed, is a regioselective reaction that provides the substitution products arising from alkylation at the more substituted allyl terminus, irrespective of the nature of the substituents on the carbon-carbon double bond. Other transition metal catalysts have exhibited this regiochemical trend, but the scope of those is limited to substrates that are phenyl-substituted so the alkylation occurs at the more electrophilic benzylic position. Moreover, iridium-catalyzed allylic alkylations also proceed to yield the *Z*-substitution products from *Z*-allyl acetates in a limited number of examples. These results are in stark contrast to palladium and molybdenum processes in which *Z*-substrates are isomerized to produce the corresponding *E*-substitution products. The stereoselectivity, although not addressed specifically in this section, follows the same trends observed with palladium and molybdenum. The ability of iridium complexes to catalyze allylic alkylations to regioselectively produce the more substituted alkylation products opens the door to asymmetric catalysis through the use of chiral ligands.

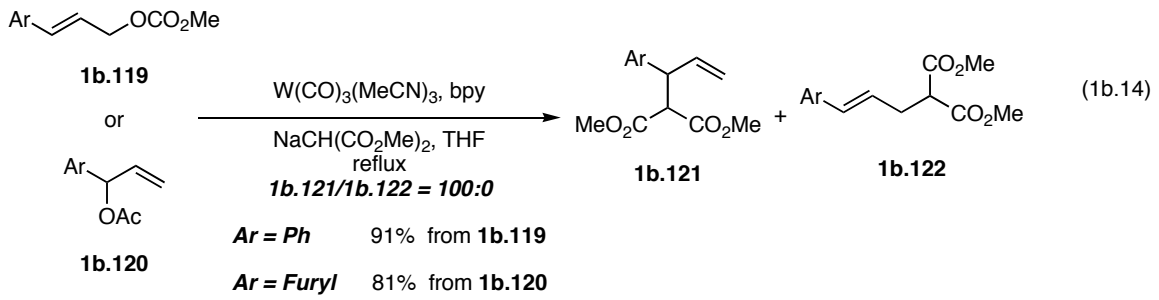
1.B.6 Ruthenium- and Tungsten-Catalyzed Allylic Alkylations

The first reports of the use of tungsten to catalyze allylic alkylations surfaced as early as 1983, in a seminal publication by Trost and coworkers.[98] A subsequent publication by Lloyd-Jones *et. al.* in 1995 elaborated on the use of a tungsten-bipyridine complex to mediate the desired transformation.[103] It was not established that ruthenium was capable of catalyzing the allylic substitution reaction until the early 1990's when Watanabe illustrated the use of Ru(η^4-1,5-cyclooctadiene)(η^6-1,3,5-cyclooctatriene), Ru(COD)(COT), as a regioselective allylic alkylation ruthenium catalyst.[99] Trost and coworkers then reported in 2002 that the cationic ruthenium species, [(η^5-

$C_5Me_5)Ru(NCMe)_3]PF_6$, catalyzed the allylic alkylation in excellent yields regioselectivity.[104]

1.B.6.1 Tungsten-Catalyzed Substitution Reactions

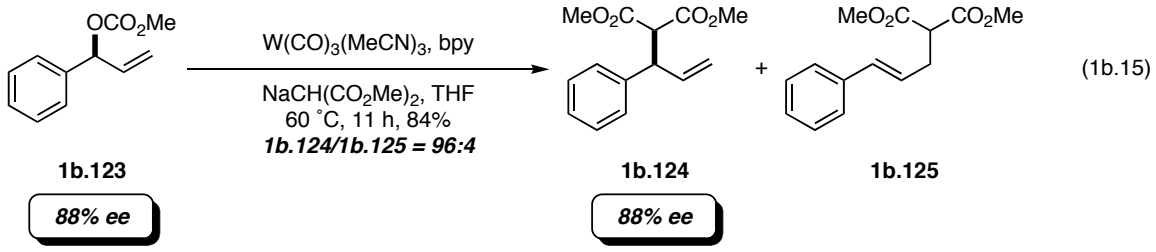
Initial reports on tungsten-mediated allylic alkylations in the early 1980's showed that allylic carbonates underwent alkylation when treated with 15 mol% $W(CO)_3(MeCN)_3$, 15 mol% 2,2´-bipyridine (bpy) and a stabilized nucleophile. The reaction was found to regioselectively provide the more substituted alkylation product.[98] Findings illustrated that $W(CO)_6$ was catalytically inactive, whereas $W(CO)_3(MeCN)_3$ showed modest reactivity (31% yield in 16 h). Efforts to enhance catalytic activity by the addition of phosphine ligands merely poisoned the catalyst. However, use of the bpy ligand led to a significant improvement in yield (65% in 18 h) presumably due to the strong π-donor capability of the bpy ligand to facilitate the opening of a coordination site on the metal. For example, treatment of either the conjugated allylic carbonate **1b.119** or the secondary allylic acetate **1b.120** with sodium dimethyl malonate in the presence of the tungsten-bypyridyl complex yielded the alkylation product **1b.121** resulting from alkylation at the more substituted allylic position (Eq. 1b.14). The aryl group was found to be critical in obtaining good regioselectivity in these cases, as alkyl substituted substrates often times gave mixtures of regioisomers, typically in a 75:25 ratio favoring the branched product.



(1b.14)

The diastereoselectivity of the process was shown to proceed with *syn* selectivity to provide the product of net retention of stereochemistry.[98] This result runs parallel to that observed with palladium and molybdenum catalysts However, whether the reaction proceeded through a double inversion sequence as is observed with palladium, or a double retention as with molybdenum to result in a net retention was not explored. The chemoselectivity was likewise examined with the tungsten-bipyridyl catalyst, and it was observed that allylic carbonates underwent substitution exclusively in the presence of a primary alkyl bromide.[98]

Lloyd-Jones and coworkers in 1995 found that the more air-stable and THF soluble tungsten complex, $W(CO)_3(\eta^6\text{-}C_7H_5)_3$, was a useful alternative to achieve identical regio- and stereoselective results in the allylic alkylation.[103] They also established that the reaction proceeded with net retention of stereochemistry. Thus, alkylation of enantioenriched carbonate **1b.123** preferentially yielded the branched substitution product **1b.124** (**1b.124/1b.125** = 96:4) in 84% yield without loss of optical purity (Eq. 1b.15). Catalyst reactivity led the authors to speculate that tungsten-catalyzed allylic alkylations did not proceed *via* the mechanism established for palladium and molybdenum. Nonetheless, conclusive mechanistic studies were not performed, and therefore remain purely speculative.



(1b.15)

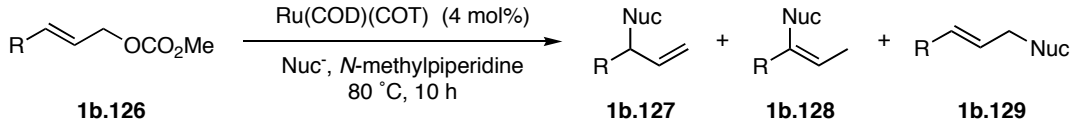
1.B.6.2 Ruthenium-Catalyzed Allylic Substitutions

Reports from Watanabe and coworkers on ruthenium-catalyzed allylic alkylations showcased the differences in product selectivity from other metal-stabilized allyl intermediates.[99] Additionally, the intermediate -ally ruthenium complexes exhibited a propensity to react as allyl nucleophiles under some conditions. Notably, by attenuating the reaction conditions in the ruthenium-catalyzed process, diallylation products were attainable, a transformation often times difficult under palladium catalysis.

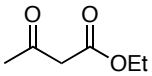
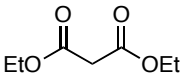
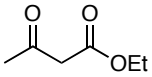
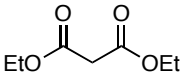
A series of allylic carbonates **1b.126** were alkylated with either a dialkyl malonate or -ketoester nucleophile to yield mixtures of three different isomers (Table 1b.6).[99] The product arising from alkylation at the more substituted allylic terminus was most often the dominant reaction product. However, presence of the isomerized product **1b.128** was observed in a few cases in which -ketoesters were used as the nucleophile (entry 1). Although the alkylation of carbonate **1b.126** with -ketoesters proved regioselective (entries 1 and 3), the use of dialkyl malonate gave equal amounts of branched **1b.127** and linear **1b.129** substitution products (entries 2 and 4). An additional finding was that diallylation of -ketoesters could be accomplished by performing the reaction with as much as a three-fold excess of allylic carbonate. Treatment of allylic carbonate **1b.130** with methyl acetoacetate in the presence of Ru(COD)(COT) provided a mixture (10:90)

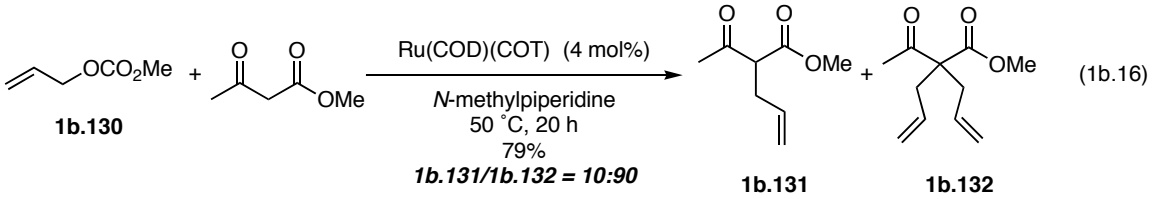
of the mono- and dilacerated products **1b.131** and **1b.132** respectively in good yield (Eq. 1b.16).[99]

Table 1b.6. Regioselectivity in the ruthenium-catalyzed allylic alkylation of **1b.126**.



1b.126 **1b.127** **1b.128** **1b.129**

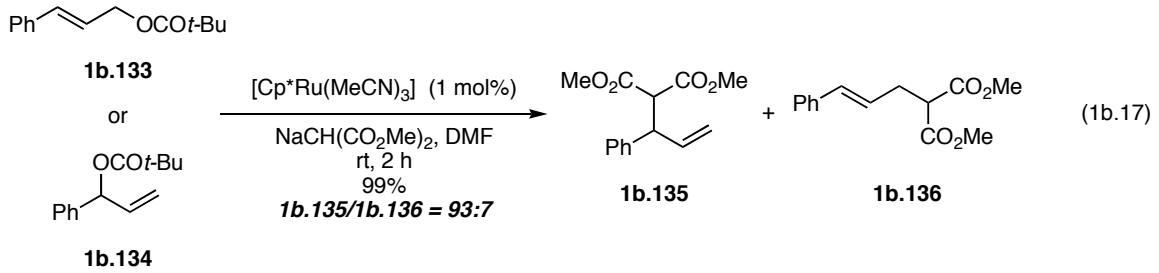
Entry	*R*	*Much*	*Yield (%)*	*1b.127/1b.128/1b.129*
1	Ph		69	93:7:0
2	Ph		52	50:0:50
3	Me		73	90:0:10
4	Me		46	50:0:50



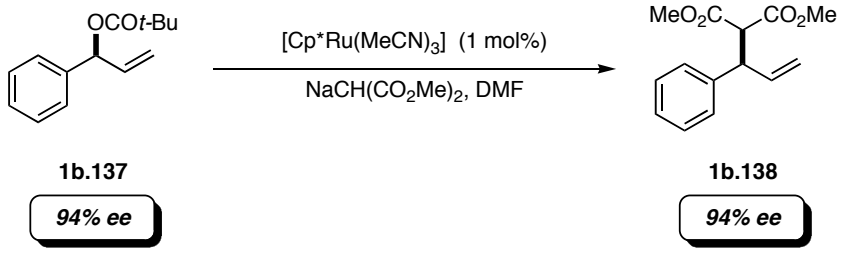
1b.130 **1b.131** **1b.132** (1b.16)

Later Trost found that when the cationic ruthenium complex [(η^5-C_5Me_5)Ru(NCMe)$_3$]PF$_6$ was used, the allylic alkylation of unsymmetrical carbonates proceeded in improved yield and with regioselectivities superior to those reported by Watanabe.[104] In general, alkylations proceeded at the more substituted benzylic terminus with regioselectivities as high as 100:1. When either the linear or branched allylic

carbonate **1b.133** or **1b.134** was allowed to react with sodiodimethyl malonate in the presence of $[(\eta^5\text{-}C_5Me_5)Ru(NCMe)_3]PF_6$ (1 mol%), the branched alkylation product **1b.135** was obtained in excellent yield (99%) and high regioselectivity (93:7) (Eq. 1b.17).[104] The catalyst also provided substitution products with complete chirality transfer, as illustrated by alkylation of the chiral carbonate **1b.137** (94% *ee*) to provide the corresponding substitution product **1b.138** (94% *ee*) (Eq. 1b.18). Nitrogen and oxygen nucleophiles were also shown to be viable components in the ruthenium-catalyzed process as illustrated by the total synthesis of (−)-fluoxetine.[104]



(1b.17)



(1b.18)

1.B.7 Rhodium-Catalyzed Allylic Alkylation

The first use of a rhodium species catalyst to promote the allylic alkylation of an allylic carbonate was reported in 1984 by Tsuji and coworkers.[105] They found that the rhodium-catalyzed process showed a weak preference in some cases, to yield the products resulting from substitution at the allylic site that originally bore the leaving

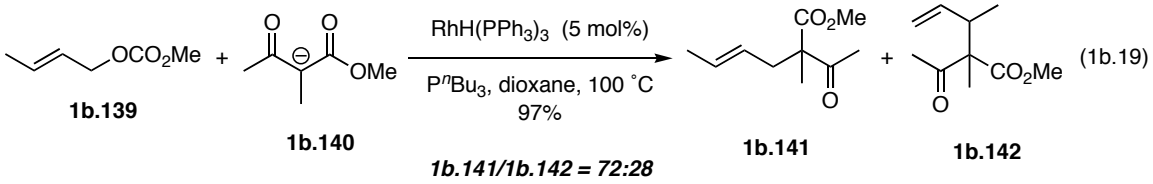
group. This regioselectivity was heretofore unseen in studies involving other metals.[105] Only two regiochemical trends had been previously observed in transition metal-catalyzed allylic alkylations. There were those in which the substitution occurred at the less sterically congested allyl terminus (as observed with palladium) or the more substituted site (preferred by molybdenum, iridium, ruthenium and tungsten catalysts). Evans and coworkers subsequently discovered a rhodium(I) complex capable of catalyzing the allylic alkylation to selectively provide substitution products resulting from alkylation at the more substituted terminus.[106] These results are in accord with those observed for molybdenum, tungsten, iridium and ruthenium.

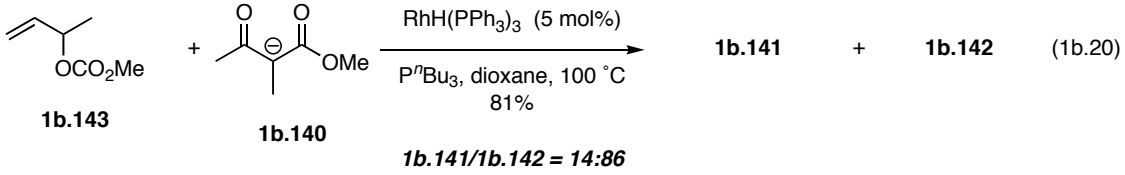
1.B.7.1 Regioselectivity

Tsuji first examined the alkylation of methyl allylcarbonate **1b.139** with β-ketoester **1b.140** in the presence of Wilkinson's catalyst, $RhCl(PPh_3)_3$. Unfortunately, this rhodium(I) complex showed little catalytic activity in effecting this transformation. The addition of phosphines (95% with P^nBu_3) and phosphates (90% with $P(OEt)_3$) enhanced the reactivity; however, yields were rather poor in some instances (15% with PPh_3, and 90% with dppe). The real improvement was observed when the rhodium(I) source was changed from Wilkinson's catalyst to $RhH(PPh_3)_4$, and the alkylation was performed in the presence of P^nBu_3 to provide the substitution product in 93% yield.[105]

With a suitable catalyst system in hand, the regioselectivity of the allylic alkylations was analyzed by screening a number of allylic carbonates. Although the products arising from substitution at the more substituted terminus were formed exclusively from the corresponding branched carbonates, two substrates provided unusual results when alkylated with β-ketoester **1b.140.** The primary allylic carbonate **1b.139** provided a mixture (72:28) of regioisomers **1b.141** and **1b.142** respectively in 97% yield

(Eq. 1b.19).[105] However, when the secondary allylic carbonate **1b.143** was treated with **1b.140** in the presence of $RhH(PPh_3)_4$ and P^nBu_3, the regioselectivity of the reaction was reversed to favor **1b.142** (regioselectivity = 86:14) (Eq. 1b.20). Hence this observed substitution at the carbon bearing the leaving group laid the groundwork for additional studies of the rhodium-catalyzed allylic alkylations.



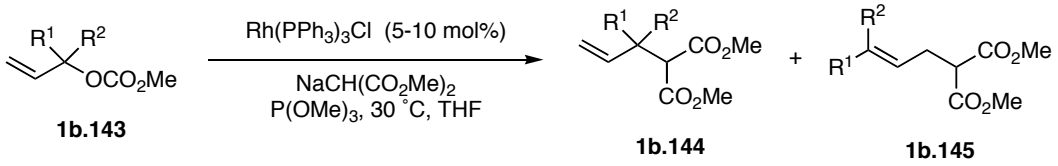


In 1998, Takeuchi described the use of $[Rh(COD)Cl]_2$ in the presence of $P(OPh)_3$ to catalyze the allylic substitution reaction.[107] Although secondary allylic carbonates underwent alkylation in good yields and regioselectivities, primary carbonates were not very selective in providing one regioisomer over another. At about the same time, Evans and coworkers reported the use of a phosphite-modified Wilkinson's catalyst complex to catalyze the allylic alkylation of a series of unsymmetrical secondary and tertiary allylic carbonates.[106]

Evans found that the triorganophosphite-modified Wilkinson's catalyst, $RhCl(PPh_3)_3/P(OMe)_3$, provided substitution products arising from alkylation at the more substituted allylic terminus (Table 1b.7).[106] Secondary allylic carbonates of the type **1b.143** provided the branched substitution product **1b.144** in excellent yield and

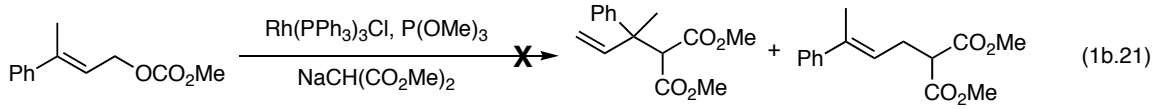
regioselectivity in each case (entries 1-3). Reactions involving tertiary allylic carbonates were substantially more sluggish. In order to achieve useful selectivities for tertiary allylic carbonates, it was necessary to increase the catalyst load to 10 mol% from the 5 mol% catalyst load required for the secondary carbonates. Less trimethylphosphite was necessary for the secondary substrates than with the tertiary analogs (entries 4 and 5). Although the yields were erratic, the regioselectivity observed in these reactions was superb, providing the branched product **1b.144** almost exclusively. Interestingly, the *c*-hexyl methyl tertiary carbonate was unreactive under the reaction conditions (entry 6). Additionally, when the primary carbonate **1b.146** was subjected to the reaction conditions, no substitution product was obtained and 95% of the starting carbonate was recovered. The authors speculate that this result indicates the reaction does not proceed *via* a direct insertion mechanism. Rather, they proposed oxidative ionization in an S_N2'-fashion, which would be difficult given the increased steric congestion of carbonate **1b.146**. The increased yield and excellent regioselectivities observed in the $RhCl(PPh_3)_3/P(OMe)_3$ complex is presumably a consequence of the increased π-accepting of the phosphite ligand that upon coordination to the rhodium center increases the rate of catalytic turnover.

Table 1b.7. Regioselectivity in the $RhCl(PPh_3)_3/(POMe)_3$-catalyzed allylic alkylation.



1b.143 **1b.144** **1b.145**

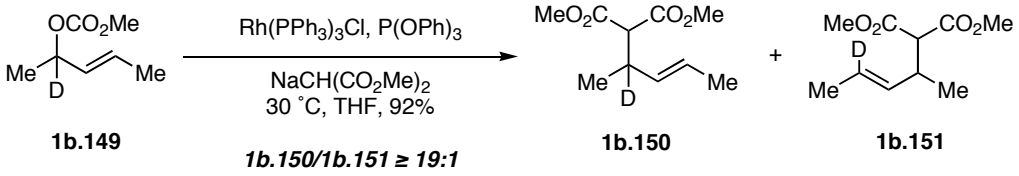
Entry	*R^1*	*R^2*	*Yield (%)*	*1b.144/1b.145*
1	H	Me	91	99:1
2	H	Ph	95	98:2
3	H	*c*-Hex	84	93:7
4	Me	Me	89	≥99:1
5	Me	Ph	32	≥99:1
6	Me	*c*-Hex	trace	□



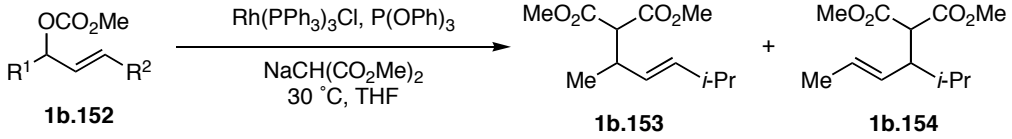
1b.146 **1b.147** **1b.148** (1b.21)

Two observations made by the Evans research group in 1998 led them to propose an alternative mechanistic hypothesis for the rhodium(I)-catalyzed allylic alkylation.[106] The first observation was that the deuterated allylic carbonate **1b.149** underwent reaction with sodium dimethyl malonate in the presence of $RhCl(PPh_3)_3/P(OPh)_3$ to produce a mixture (≥19:1) of substitution products **1b.150** and **1b.151** in 92% yield favoring

alkylation at the carbon that bore the leaving group (Eq. 1b.22). Similarly, alkylation of unsymmetrical carbonates **1b.152a/b** provided the formal direct substitution products **1b.153** and **1b.154** in a 97:3 ratio.[106] The authors suggested that these results illustrate the rhodium(I) species generated *in situ* was capable of exhibiting a "memory effect" with regards to leaving group departure and the site of alkylation (Eq. 1b.23). However, this level of selectivity was only observed when $RhCl(PPh_3)_3$ was modified with $P(OPh)_3$ and not $P(OMe)_3$. The experiments with carbonates **1b.149** and **1b.152** seem to indicate that, unlike the other transition metal-stabilized intermediates, the allylrhodium species does not equilibrate prior to alkylation, and therefore a common intermediate is not encountered when allylically transposed carbonates are alkylated. Therefore, it appears that the presence of $P(OPh)_3$ slows the rate of equilibration between allylmetal intermediates.



(1b.22)



(1b.23)

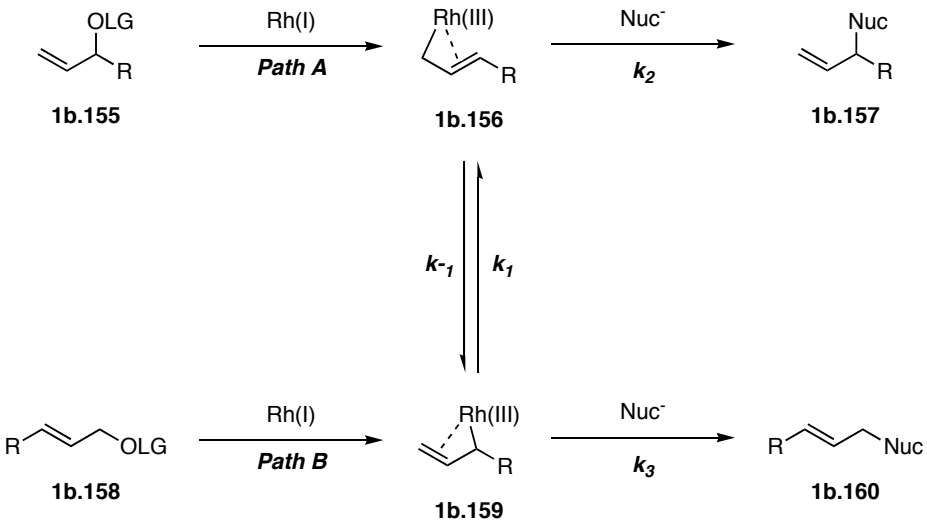
a: R^1 = Me, R^2 = ^{i}Pr 83% **1b.153/1b.154** = 97:3

b: R^1 = ^{i}Pr, R^2 = Me 87% **1b.153/1b.154** = 3:97

In order to account for the unusual regioselectivity Evans and Tsuji observed in these experiments, Evans proposed that the rhodium-catalyzed allylic alkylation reaction proceeded through an *enyl* (□+π) intermediate rather than the π-allyl complex thought to

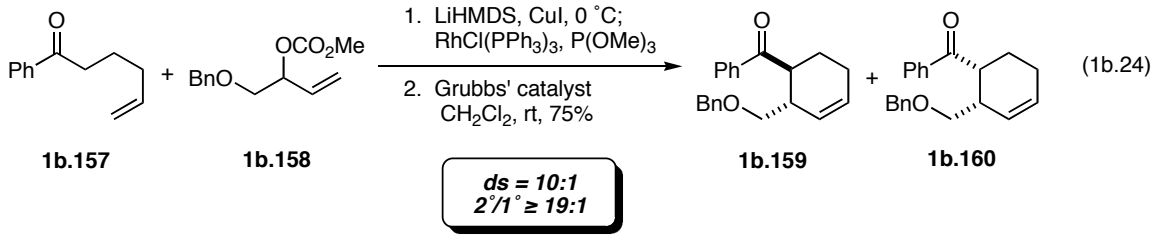
be involved in other transition metal-catalyzed allylic alkylations (Scheme 1b.14).[106] Upon rhodium(I) complexation and subsequent oxidative ionization to a secondary allylic substrate **1b.155**, an *enyl* intermediate **1b.156** was presumably formed. This could undergo alkylation by the nucleophile in an S_N2'-like fashion to yield the product of direct substitution **1b.157**. Alternatively, **1b.157** may undergo □□□□□ isomerization to yield *enyl* intermediate **1b.159**, which when treated with the nucleophile provides the linear substitution product **1b.161a.** Likewise, the primary allylic substrate **1b.158** would react *via* intermediate **1b.159**, which can either undergo substitution to provide **1b.160** or isomerize to *enyl* **1b.156**. Nucleophilic attack (k_2) to **1b.156** is in all probability faster than isomerization (k_{-1}) due to the relative stability of intermediate **1b.156** in comparison to **1b.159**. The equilibrium position of the two intermediates is based on the influence of substituents on the ally moiety and their influence on the position of the transition metal ($k_1 >> k_{-1}$). However, in the absence of any overriding steric or electronic substituent effects, the allylic alkylation should proceed to give the direct substitution product without isomerization of the *enyl* intermediates.

Scheme 1b.14



1.B.7.2 Stereoselectivity

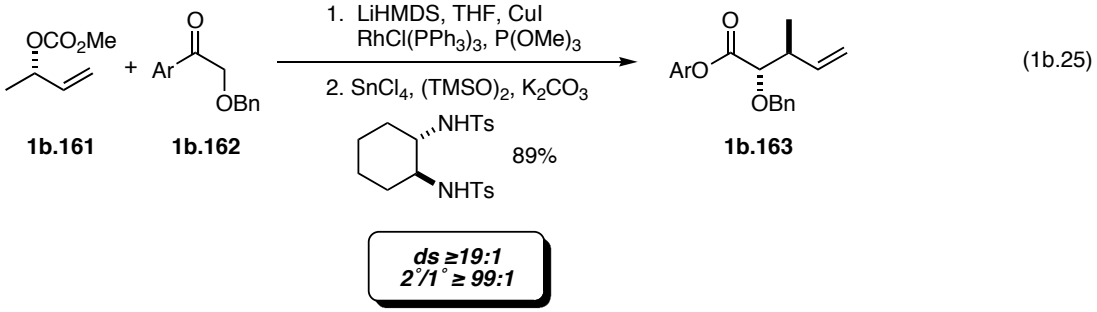
Evans then expanded the scope of the rhodium(I)-catalyzed allylic alkylation to include acyclic unsubstituted[33] and α-alkoxy-substituted[108] copper(I) enolates as nucleophiles. The use of unstabilized enolates in the allylic substitution reaction dramatically enhances the synthetic utility of the method by enabling the use of more structurally diverse nucleophiles. The use of hard nucleophiles in transition metal-catalyzed allylic alkylations has suffered from a number of limitations associated with regiochemical inconsistency.[109] To overcome the inherent drawbacks to this class of nucleophiles, Evans attenuated the hardness of the alkali metal enolate salt by transmetallation with a copper(I) salt, thereby rendering the anion softer.[33] When ketone **1b.161** was treated with LiHMDS, transmetallated with CuI, then treated with allylic carbonate **1b.162** in the presence of $RhCl(PPh_3)_3/P(OMe)_3$, the secondary substitution product was obtained in a regioisomeric ratio ≥19:1 (Eq. 1b.24). Subsequent ring closing metathesis with Grubbs' ruthenium catalyst yielded a mixture (10:1) of the *anti* and *syn* cyclohexene products **1b.163** and **1b.164**.[33]



(1b.24)

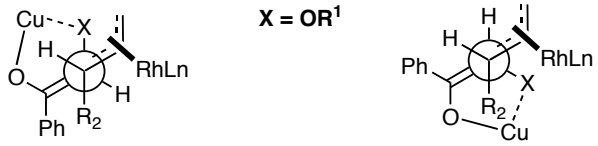
In a subsequent report, Evans illustrated how acyclic α-alkoxy-substituted copper(I) enolates could be used as nucleophiles in the allylic substitution reaction catalyzed by $RhCl(PPh_3)_3/P(OMe)_3$.[108] One of the key features of this method is the high diastereoselectivity observed in the alkylation of unsymmetrical allylic carbonates.

Alkylation of carbonate **1b.165** with the copper enolate of α-benzyloxyketone **1b.166** in the presence of $RhCl(PPh_3)_3/P(OMe)_3$, followed by Baeyer-Villiger oxidation[110,111] provided ketone **1b.167** in excellent yield and regio- and diastereoselectivity (Eq. 1b.25).[108] The authors proposed that the acyclic diastereocontrol was obtained *via* a *Z*-chelated enolate **1b.168** that avoids an unfavorable eclipsing interaction between the copper metal the substituent R^2 present in **1b.169** (Figure 1b.1). This constitutes a regio- and diastereoselective method to alkylate unsymmetrical allylic alcohol derivatives with acyclic α-alkoxy-substituted enolates.



(1b.25)

Figure 1b.2. Proposed transition states for the observed diastereoselectivity in Eq. 1b.25

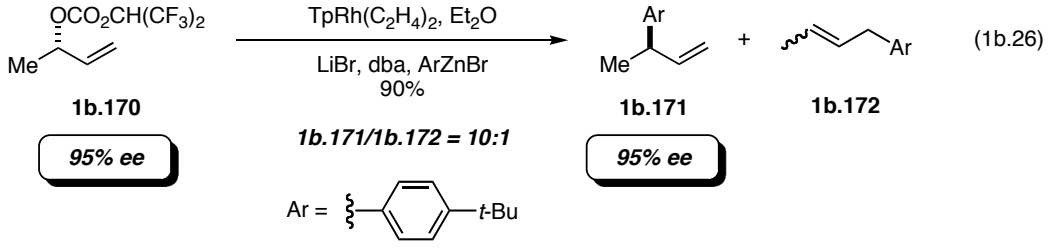


1b.168 ***Favored TS***

1b.169 ***Disfavored TS***

The scope of the rhodium(I)-catalyzed allylic alkylation was further expanded in 2003 by Evans when he reported the use of organozinc halides to alkylate unsymmetrical allylic alcohol derivatives regioselectively.[112] When the enantioenriched allylic fluorocarbonate **1b.170** was treated with the arylzinc bromide in the presence of

$TpRh(C_2H_4)_2$ (Tp = hydrotris(pyrazolyl)borate), LiBr and dibenzylideneacetone (dba) at 0 ˚C, a mixture (10:1) of the arylated products **1b.171** and **1b.172** was obtained in 90% yield (Eq. 1b.26). Interestingly the reaction proceeded without loss of optical purity to provide **1b.171** in 95% *ee*, but an *inversion* of absolute configuration was observed. The stereochemical outcome of this process is most likely a result of an *anti-syn* mechanism in which the rhodium catalyst ionizes the allylic carbonate in an *anti* fashion, the aryl group is transferred to the rhodium(III) species by transmetallation followed by reductive elimination in a *syn* manner to provide an overall inversion of absolute configuration.



1.B.7.3 Summary

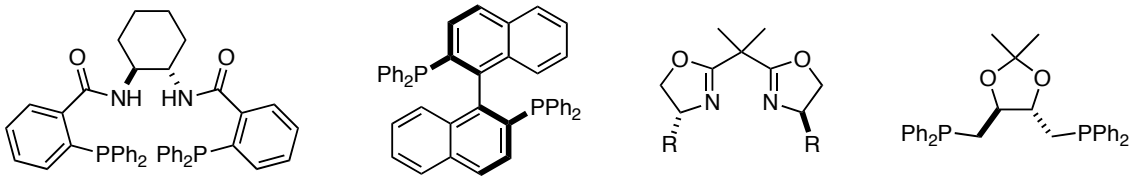
The Evans' research group pioneered the use of π-allylrhodium chemistry by developing a high yielding, regioselective method enabling the allylic alkylation of unsymmetrical allylic carbonates. The development of this class of allylic alkylations raises serious questions as to the nature of the allylmetal intermediates due to the observation that limited examples involving $P(OPh)_3$ a "memory effect" was observed resulting in substitution products in which the nucleophile becomes bonded to the carbon bearing the leaving group. The authors propose that this indicates a slow isomerization of allylrhodium intermediates in the absence of overriding substituent effects that often dictated the regiochemical outcome in molybdenum-, tungsten- and iridium- catalyzed processes. The scope of the procedure was expanded by using heteroatom (phenols[45] and

sulfonamides[53]), unstabilized copper(I) enolates and organozinc halide nucleophiles as viable components in the overall carbon-carbon bond forming event. The reaction proceeded with net retention of absolute configuration in the allylic alkylation of enantioenriched allylic carbonates with stabilized nucleophiles, net inversion of configuration when treated with unstabilized aryl zinc reagents, and unique diastereocontrol in sequential allylic substitutions to allow for control of 1,3-stereochemistry.[113]

1.B.8 The Transition Metal-Catalyzed Enantioselective Allylic Alkylation

More recent advances in the realm of allylic alkylations have led to the development of enantioselective variants. When chiral ligands are present on the catalyst, the metal species then becomes an asymmetric manifold by which the overall process can be rendered enantioselective. The majority of the work by far has been focused on palladium-based chiral templates,[5,13] although significant advances have been made using molybdenum,[114-118] and reports have also surfaced using tungsten[119], iridium[101] and rhodium.[120] Some of the most common ligands used for these asymmetric transformations are depicted in Figure 1b.3. Ligand **1b.173** is most commonly referred to as the "Trost ligand" named for its discoverer. The BINAP[121,122] (**1b.174**) and DIOP[123] (**1b.176**) ligands, although extremely useful for enantioselective hydrogenations, have shown limited utility in asymmetric allylic substitutions. Likewise, the bisoxazoline **1b.175** ligands have also exhibited limited asymmetric induction in allylic alkylations.

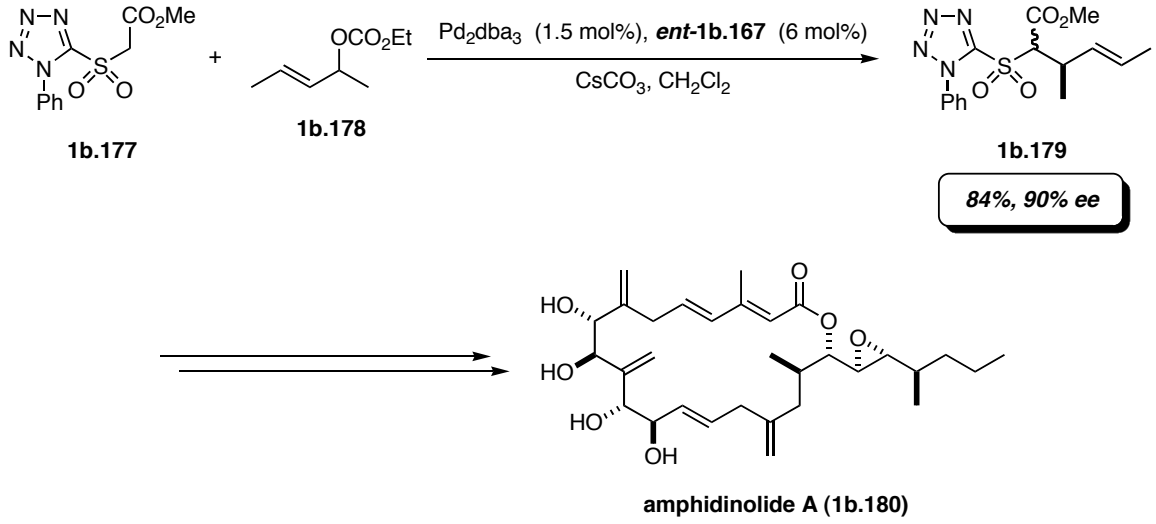
Figure 1b.3. Chiral ligands employed in asymmetric allylic alkylations.



1b.173 **1b.174** **1b.175** **1b.176**

An notable example of the use of an asymmetric allylic alkylation in the total synthesis of a complex natural product is illustrated by synthesis of the macrolide amphidinolide **1b.180** (Scheme 1b.15).[124] The approach featured assembly of the chiral side chain employing the asymmetric allylic alkylation of *meso*-allylic carbonate **1b.178** with sulfone ester **1b.177** in the presence of ligand ***ent*-1b.173** to provide the alkylation product **1b.179** in 90% *ee* and as a mixture (1:1) of diastereomers. This disconnection led to an efficient, atom economical approach to this complex natural product.

Scheme 1b.15



1b.177 **1b.178** **1b.179**

amphidinolide A (1b.180)

This discussion on the enantioselective variant of transition metal catalyzed allylic substitutions is brief, and the reader is encouraged to consult any number the reviews cited on the subject for further information. Although the asymmetric allylic alkylation has been around for quite some time, relatively little has been accomplished using the vast array of allylic alkylation catalysts capable of mediating the carbon-carbon bond forming event. The future of this transformation may lie in the development of new chiral ligands for different metal templates to combine asymmetry with the catalyst's unique regio-, chemo- and stereoselectivity to achieve the synthesis of previously problematic target structures. Due to its broad applicability the synthetic community should witness greater application of the asymmetric variant of the allylic alkylation with each coming year.

1.B.9 Overall Summary of Section 1.B

Although particularly succinct in covering the enormous volume of work that has been presented over the past 30-35 years on transition metal-catalyzed allylic alkylations, this discussion should afford the reader with a broad sense of what can be accomplished with the different transition metals capable of forming π-allyl intermediates from ionizable allylic substrates. The issue of regioselectivity in the allylic alkylation is quite possibly the defining factor that separates one catalyst system from another. Also, the mechanistic rationales and hypotheses set forth by the prominent researchers in the field have provided a wealth of intellectual discussion on the origin of the three different types of regioselectivity observed.

There are three general regiochemical trends observed in the transition metal-catalyzed allylic alkylation. The first arises as a result of primarily steric effects to yield substitution products arising from alkylation at the less hindered allyl terminus, as

exemplified by palladium catalysis. Second, electronic factors play the dominant role in product distribution yielding alkylation at the more substituted allylic carbon, as observed with molybdenum, tungsten, iridium, ruthenium and with most rhodium catalysts. Finally, there have been limited reports in rhodium-catalyzed allylic alkylations of substitution occurring at the site of leaving group departure resulting in a formal direct substitution reaction. Transition metal catalysts have been sufficiently developed to address the first two of these regiochemical trends with broad scope and utility with regards to the allylic substrate and nucleophile. However, a catalyst which showed a general propensity for formal direct substitution of the leaving group had yet to be discovered.

The stereoselectivity exhibited in the allylic alkylation proved quite general regardless of the metal complex used. In each case, alkylations with stabilized anions provided overall net retention of configuration. Most catalysts are thought to proceed *via* an *anti-anti* mechanism, except in the case of molybdenum which was shown to go through a *syn-syn* pathway. To stay competitive with the catalysts known to mediate this process, any new transition metal complexes should at least allow for the reaction to proceed without loss of enantiopurity.

In the future, studies on the allylic substitution reaction may be classified not only by the substrates involved, but by the transition metal used to catalyze it, the overall stereoselectivity throughout the reaction and the synthetic utility of the alkylation products. There is still the potential to explore the origin of, optimize to a useful synthetic level, and determine the scope of various combinations of the selectivities enjoyed by each transition metal catalysts in the development of novel processes. Additionally, given the number of different reactions some allylic alkylation catalysts mediate, the potential for developing cascade reaction sequences should be a major area

of emphasis in future studies. These opportunities should maintain the transition metal-catalyzed allylic alkylation as one of the most vigorously studies and useful reactions in modern synthetic organic chemistry.

1.C TRANSITION METAL-CATALYZED CARBOCYCLIZATION REACTIONS

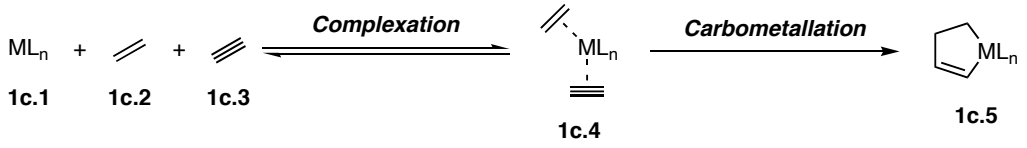
1.C.1 Introduction

The term "carbocyclization" has been used extensively in recent years to describe those cyclizations that involve a carbon-carbon bond forming event to close a ring, which is often mediated by a transition metal catalyst.[125] These types of reactions are typically distinguished by the formation a metallocycle intermediate. The presence of this metal-stabilized species separates these annulations from those which proceed through radical intermediates and those initiated by thermal or photochemical means. Given such a broad definition, it comes as no surprise that a wide variety of transformations fit this loose criteria. Cyclopropanations,[126] annulations including the Pauson-Khand reaction,[127,128] the Heck reaction,[129-132] and numerous [*m*+*n*+*o*] cycloadditions fall into this category of transformations.[125] A number of different metal species exist that are capable of catalyzing these reactions. Palladium-mediated transformations[129,133,134] have been one of the more widely studied classes, although ruthenium, rhodium, titanium, and molybdenum have seen applicability as well.[125]

The overall process typically involves a specific carbometallation event. The transition metal catalyst transfers one carbon atom-containing fragment across either a carbon-carbon double bond or triple bond to form the metallocycle intermediate. Often times the fragment **1c.2** transferred by the catalyst **1c.1** to the original π-system **1c.3** *via* intermediate **1c.4** is a carbon-carbon double or triple bond (Scheme 1c.1). Formation of

the five-membered metallocycle **1c.5** occurs upon carbometallation. If the alkene and alkyne depicted in Scheme 1c.1 are tethered, the reaction then becomes intramolecular, and a carbocyclization event ensues. Given the enormous volume of published work on transition metal-catalyzed carbocyclization reactions[125] the discussion herein will be limited to asymmetric cyclopropanations,[126,135-137] [5+2] cycloadditions,[138] Pauson-Khand annulations[127,128,139] and cycloisomerizations.[133,134,140] In the context of these transformations, only the most widely used catalysts which provide superior results will be addressed.

Scheme 1c.1

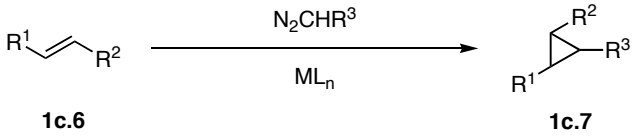


1.C.2 Transition Metal-Mediated Asymmetric Cyclopropanation Reactions

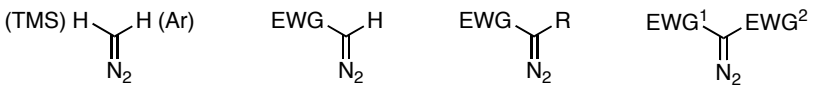
The cyclopropanation of olefins *via* transition metal-catalyzed decomposition of diazoalkanes has long been recognized as a critical tool in the synthesis of complex natural products.[126,141,142] The study of the cyclopropane subunit has been the focus of many research groups for a number of years due to the synthetic potential incorporated into the small, strained carbocycle. Attempts to synthesize this highly-strained cycloalkane subunit has led to many approaches. A main thrust in recent decades has been the development of highly diastereo- and enantioselective process for the synthesis of cyclopropanes.[143-146] The ligation of chiral entities on the surface of transition metal catalysts generate a chiral "template" through which the desired cyclopropanation reaction is rendered asymmetric.[126] Diazoalkanes are typically substrates of choice in this

process due to their ease in preparation and reactivity.[136,147] In general, diazoalkanes of type **1c.8-1c.11**, which differ only in their various electronic properties, are treated with a transition metal catalyst in the presence of an alkene **1c.6** to form the desired cyclopropane **1c.7**. The relative stereochemistry of the cyclopropanation is often determined by the geometry of the carbon-carbon double bond and the substituents occupying the allyl or homoallyl positions along the chain (Scheme 1c.2). The absolute stereochemistry is thereby dictated by the chiral ligands on the metal catalyst.

Scheme 1c.2



1c.6 **1c.7**

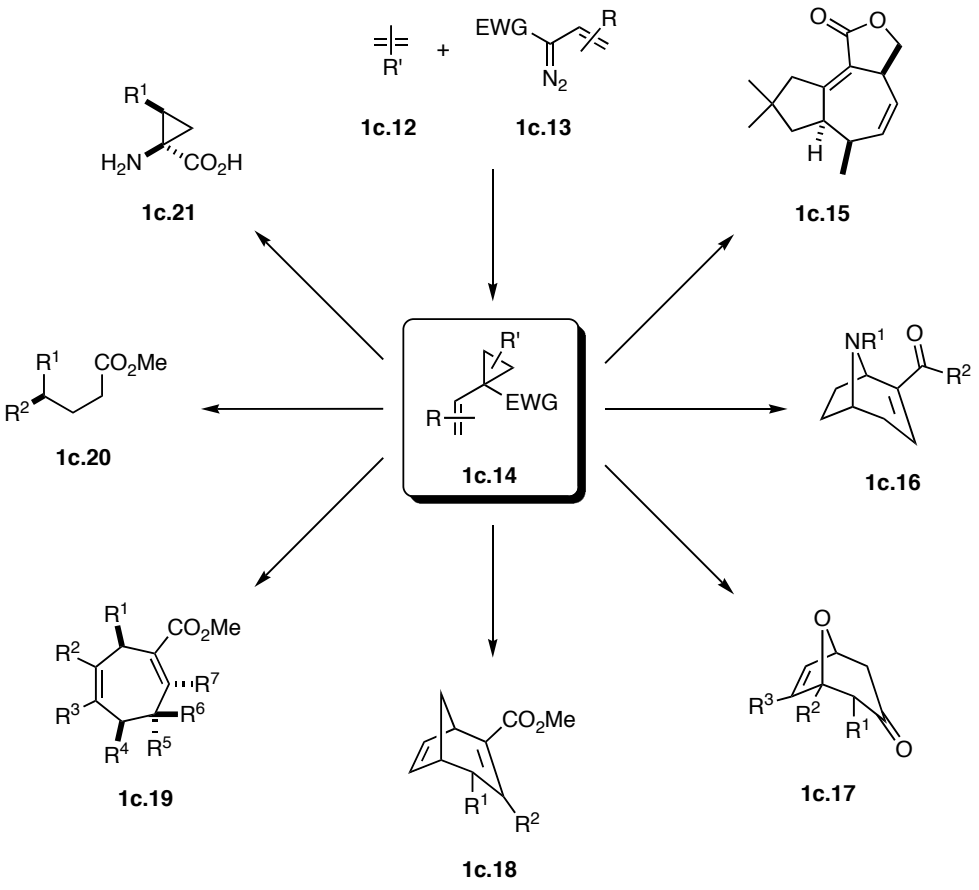


1c.8 **1c.9** **1c.10** **1c.11**

Substrates of the type **1c.10** in which the R group is vinyl provide vinylcyclopropanes that may serve as intermediates in the synthesis of more functionalized cyclic[148-151] and acyclic[152,153] alkanes. Vinylcyclopropanes **1c.14** are obtained by diazodecomposition of **1c.13** to yield a vinylcarbenoid species that upon subsequent reaction with alkene **1c.12** provides the desired product (Scheme 1c.3).[154,155] In much of the early work on cyclopropanations utilizing diazoesters, carbenoids derived from **1c.13** had shown limited utility, suffering from low yields and poor stereoselectivity.[156] Additionally, the vinyldiazomethane precursors are notoriously difficult to handle, often times rearranging to 3*H*-pyrazoles.[157] However, subsequent

work reported by Davies showed that rhodium(II) acetate facilitated the cyclopropanation of vinyldiazoesters **1c.13** to yield vinylcyclopropanes **1c.14**.[158] The synthetic utility of the reaction was expanded by placing a diene moiety in place of the simple alkene in **1c.11c.** The intermediate vinylcyclopropane would then undergo a Cope rearrangement to access bicyclic compounds **1c.15-1c.19**.[158,159] Products arising from ring opening of cyclopropane **1c.20** as well as simple, enantioenriched cyclopropanes are also obtained from this process.[160]

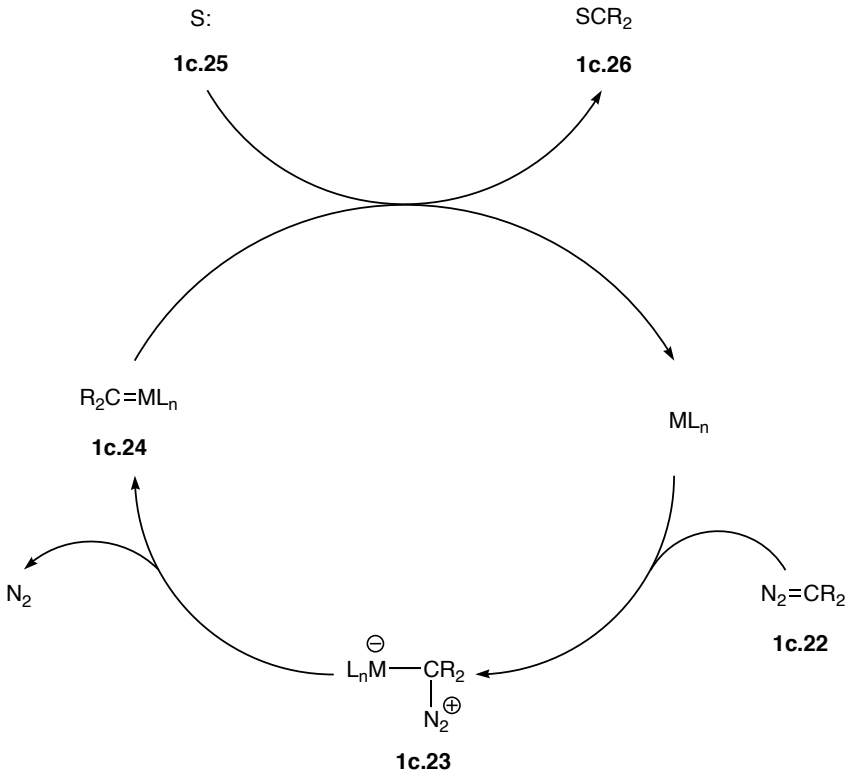
Scheme 1c.3



The generally accepted catalytic cycle for the cyclopropanation of olefins *via* diazodecomposition is illustrated in Scheme 1c.4.[135] Electrophilic addition of a

coordinatively unsaturated transition metal catalyst to the diazo compound **1c.22** produces a transient electrophilic metal carbene **1c.23** as first proposed by Yates in 1952.[161] Subsequent loss of dinitrogen provides the metal-stabilized carbene **1c.24**, which undergoes cyclopropanation with an electron rich substrate **1c.25**. Transfer of the carbene center from the metal to the substrate completes the catalytic cycle.

Scheme 1c.4



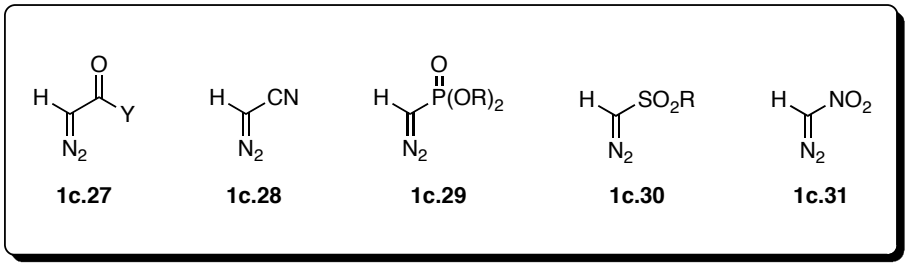
The focus of this section will rest heavily on asymmetric cyclopropanations catalyzed by either chiral copper or rhodium complexes. Additionally, different variants will be addressed to provide the reader with a succinct overview of the multitude of study that has been incorporated into this area of synthetic chemistry. Although a number different catalysts and ligand combinations have been reported for various substrates, the

goal of this discussion is to provide the reader with a broad overview, providing a reference from which more in-depth analysis can be undertaken if so desired.

1.C.2.1 Intermolecular Cyclopropanations

The most common substrates for intermolecular cyclopropanations are α-diazoesters of the type **1c.27** (Y = OR).[136,147,162] However, a number of similar compounds **1c.28-1c.31** have been shown to be viable substrates in the asymmetric cyclopropanation reaction (Figure 1c.1).[163-167] Diazosubstrates containing just one electron withdrawing group, such as α-diazoester **1c.27**, proved to be excellent substrates in intramolecular and intermolecular reactions with a wide array of catalysts. The reaction of diazoesters with achiral alkenes is one of the most studied asymmetric reactions in past decades. Issues of diastereo- and enantioselectivity have been critically examined and comprise the forefront of studies to date.[147]

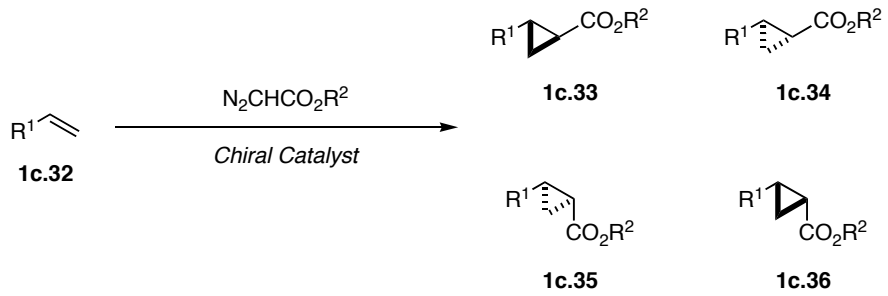
Figure 1c.1. Typical α-diazo reagents used in intermolecular cyclopropanations.



In general, alkene **1c.32** will react with the diazodecomposition product of a diazoester and transition metal catalyst such that the cyclopropanation event can potentially provide one of four possible cyclopropanes **1c.33-1c.36** (Scheme 1c.5). Typically, the field of products can be halved if one chooses the appropriate alkene and diazoester combination to maximize the *trans*/*cis* ratio of diastereomers. In many cases, an appropriate R^1 substituent on the alkene substrate or the use of a bulky ester group R^2

on the diazoester in conjunction with the catalyst can heavily influence the diastereomeric ratio of the cyclopropanation through a number of steric and electronic factors.[168] The addition of chiral ligands to the reaction mixture can further simplify the situation by rendering the overall transformation enantioselective.

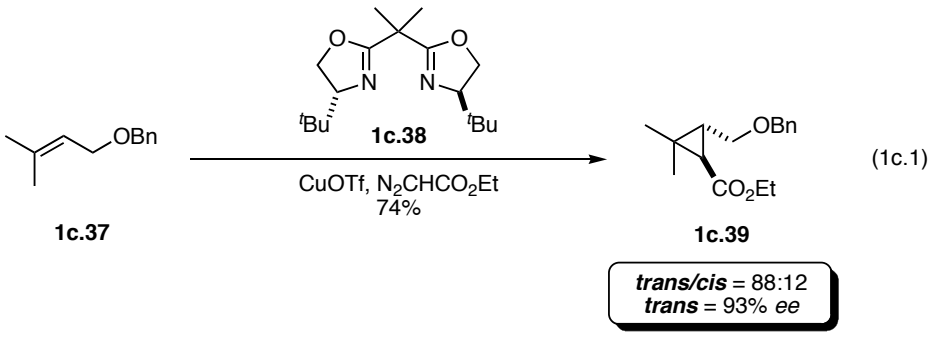
Scheme 1c.5



A number of catalysts have been shown to provide the resulting cyclopropanes in good yields and selectivity in the intermolecular reaction. The catalysts that have been shown to be the most effective are copper-, rhodium-, ruthenium- and cobalt based species.[168] Overall, copper(I) salts provide the best combination of *trans*/*cis* ratio of products with good to excellent enantiomeric excesses.[169,170] Additionally, copper seems to enjoy a broader substrate scope than do other metal catalysts. Rhodium has also been shown to be an extraordinary cyclopropanation catalyst. However, in intermolecular reactions, the rhodium catalysts examined have yielded moderate *trans*/*cis* ratios and low *ee*'s.[171] On the other hand, cobalt has been shown to be quite *cis* selective, but the catalysts are not easy to prepare due to the complexity of the ligands required.[172]

A vast array of ligands have been developed for the copper-catalyzed asymmetric cyclopropanation. Evans reported the use of bis(oxazoline) ligand **1c.38** as an extremely efficient chiral ligand.[173] Due to the success enjoyed by **1c.38**, this ligand has been used as the benchmark standard from which subsequent bis(oxazoline) ligands are measured

against to compare efficiency and selectivity.[170] The scope of substrates in the copper(I)-catalyzed transformation is quite broad. It has been demonstrated that highly substituted alkenes,[170] cyclic silyl enol ethers[174] and vinyl halides[175] are well tolerated. For example, cyclopropanation of allyl ether **1c.37** with ethyl diazoacetate in the presence of CuOTf and ligand **1c.38** provided cyclopropane **1c.39** in 74% yield, good *trans*/*cis* ratio (88:12) and excellent enantiomeric excess (93% *ee*) (Eq. 1c.1).[176]

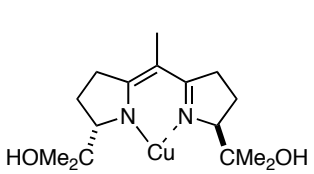


(1c.1)

In recent years, a number of ligands have been developed that are capable of inducing asymmetry in copper-catalyzed cyclopropanation reactions. Nozaki was the first to report the use of an *N*-benzylethylamine-based chiral salicylaldimino complex to cyclopropanate styrene with ethyldiazoacetate albeit in a mere 6% *ee*.[177] Over the next 40 years, a plethora of ligands, some with small and others with significant structural variations on Nozaki's ligand, have been reported to catalyze this reaction. Just a few examples of such ligands are illustrated in Figure 1c.2. Pfaltz reported in the mid-1980's that semicorrin-type ligand **1c.40** provided good dr's and excellent *ee*'s of each diastereomer in the cyclopropanation of styrene with menthyl diazoacetate.[178,179] Unfortunately this class of ligands suffers from low yields with unactivated alkenes due to the poor Lewis acidity of the ligands. Ligands **1c.41**,[180] **1c.42**[181] and **1c.43**[182] represent just two of the many bis(oxazoline) ligands and other bidentate ligands capable of

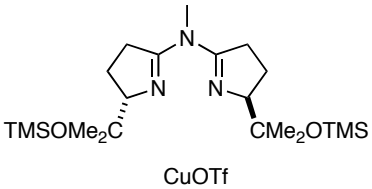
catalyzing cyclopropanations with excellent results. Bipyridine-type ligands such as **1c.44** have also been shown to be effective in providing good *trans*/*cis* ratios and enantioselectivities.[183,184]

Figure 1c.2. Chiral Catalysts Used for the Asymmetric Cyclopropanation of Styrene



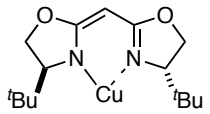
1c.40

dr = 82:12 (N_2CHCO_2*d*-menthyl)
trans = 97% *ee*, ***cis*** = 95% *ee*



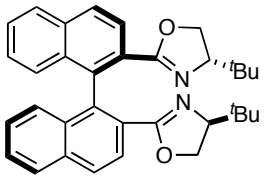
CuOTf
1c.41

dr = 84:16 (N_2CHCO_2*d*-menthyl)
trans = 98% *ee*, ***cis*** = 99% *ee*



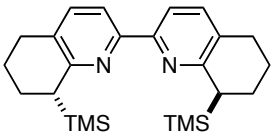
1c.42

dr = 86:14 (N_2CHCO_2*l*-menthyl)
trans = 98% *ee*, ***cis*** = 96% *ee*



$CuOTf\cdot(PhH)_{0.5}$
1c.43

dr = 68:32 (N_2CHCO_2*l*-menthyl)
trans = 95% *ee*, ***cis*** = 97% *ee*

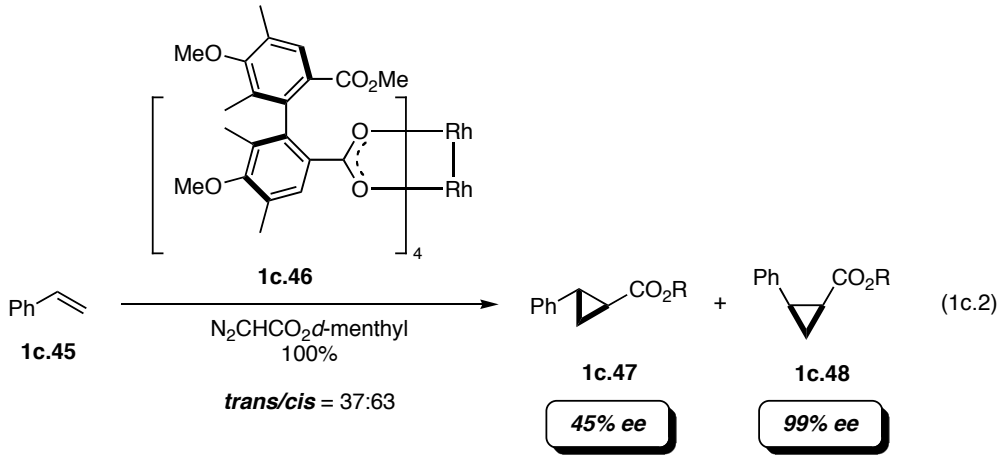


$CuOTf\cdot(PhH)_{0.5}$
1c.44

dr = 86:14 (N_2CHCO_2*t*-Bu)
trans = 92% *ee*, ***cis*** = 98% *ee*

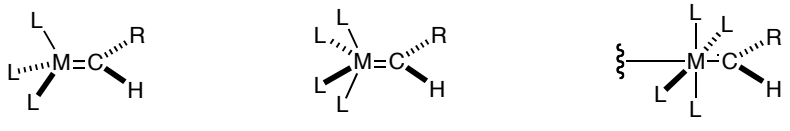
Rhodium-catalyzed cyclopropanations have also found great applicability, but intramolecular variants often suffer from poor diastereoselectivity. As shown in Eq. 1c.2, the cyclopropanation of styrene with menthyl diazoacetate in the presence of the chiral dirhodium catalyst **1c.46** provided a mixture (37:63) of cyclopropanes **1c.47** and **1c.48** in 45% *ee* and 99% *ee* respectively.[185] In a few cases, the *cis* diastereomers can be produced selectively in good *ee* to provide an option for the asymmetric synthesis of *cis* cyclopropanes.[186] The rhodium-bound carbene is one of the more reactive carbenoid species when compared to other metals. However, in general the level of

diastereocontrol is quite low in comparison.[171] This lack of selectivity has led to the limited employment of rhodium catalysis in intermolecular cyclopropanations.



Although the utility of chiral rhodium catalysis in enantioselective intermolecular cyclopropanation reactions has been limited, a number of catalysts developed provide useful levels of enantioselective induction in intramolecular cyclopropanations and C-H insertions. The early transition state for such processes indicate that the chiral environment, as dictated by the ligands on the metal, must extend out to if not beyond the electrophilic carbene carbon. Therefore the spatial arrangement of the ligands should play a key role in the asymmetric induction. Figure 1c.3 illustrates three different metal geometries **1c.49-1c.51** in which the chiral ligands may orient themselves. As can be seen, the octahedral arrangement of structure **1c.51** places the ligands on the metal nearest to the reacting carbene center.[155]

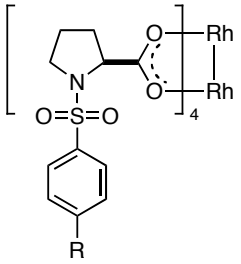
Figure 1c.3. Carbene-bound transition metal geometries.



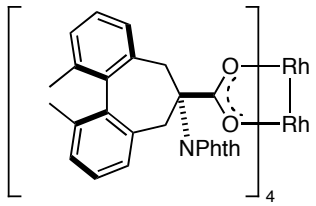
The ligands having found broad applicability in rhodium-catalyzed processes can be divided into two classes, dirhodium(II) carboxylates **1c.52-1c.57** (Figure 1c.4)[187-189] and carboxamides **1c.58-1c.88** (Figure 1c.5).[171,190-192] Prolinate derived carboxylate catalysts **1c.52-1c.54** encompass the vast majority of successful ligands in this category. One general observation is that the *N*-arylsulfonyl group seems to be a critical structural requirement for useful enantioselectivities.[160] Although the phthalamide derivatives of phenylalanine **1c.57** gave improved results over other dirhodium catalysts in asymmetric cyclopropanations, it has been shown to be a more effective chiral ligand in C-H insertion reactions.[193] The catalysts shown are dimeric, and are presumed to maintain this dimeric structure throughout the course of the reaction. Each catalyst contains four bridging carboxylate ligands allowing for coordination of the substrate to the axial sites on the metal center that is where metal carbene formation is thought to occur.

Figure 1c.4. Chiral dirhodium(II) carboxylate ligands for asymmetric cyclopropanations.

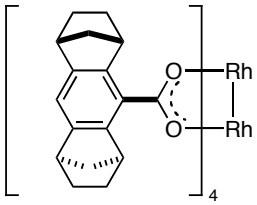
Dirhodium(II) Carboxylates:



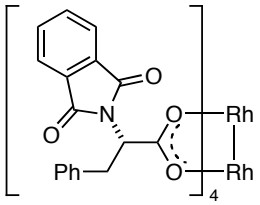
1c.52 R = H Rh_2[2*S*-BSP]$_4$
1c.53 R = ^{t}Bu Rh_2[2*S*-TBSP]$_4$
1c.54 R = $C_{12}H_{26}$ Rh_2[2*S*-DOSP]$_4$



1c.55



1c.56



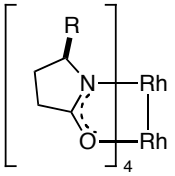
1c.57

Chiral dirhodium(II) carboxamidates have enjoyed widespread utility in enantioselective cyclopropanations. Complexes developed by Doyle and coworkers over the past couple of decades have been shown to be applicable in the synthesis of biologically active natural products.[137,155,171,191,194-196] Each catalyst is dimeric in nature, as seen in the carboxylate series **1c.52-1c.57**. However, the catalysts all contain four bridging carboxamides with a nitrogen and oxygen from each ligand bound to the metal (Figure 1c.5). Additionally, the spatial arrangement around the metal center is such that two nitrogens are adjacent to each other. The arrangement that places the stereogenic center within the ligand moiety □ to the metal-bound nitrogen atom allows for the R group to extend out from the catalyst center toward the electrophilic carbene. As in the dirhodium(II) carboxylate catalysts, the axial coordination sites are free, and it is there

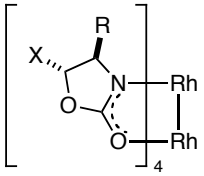
that carbene formation is thought to occur. The four types of carboxamide ligands depicted in Figure 1c.5 are most effective in asymmetric catalysis involving metal carbene formation.[126,136] What separates these catalysts from conventional ligand design is that the focus does not involve incorporating steric interactions to control enantioselectivity, but to includes dipolar influences and electrostatic effects to obtain an optimal ligand design.

Figure 1c.5. Chiral dirhodium(II) carboxamidate ligands.

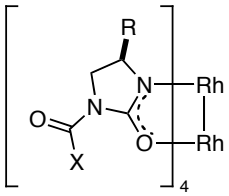
Dirhodium(II) Carboxamides:



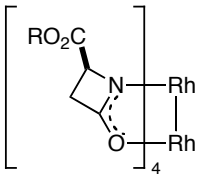
1c.58 R = CO_2Me Rh_2[5*S*-MEPY]$_4$
1c.59 R = CO_2Et Rh_2[5*S*-NEPY]$_4$
1c.60 R = $CO_2(CH_2)_{17}Me$ Rh_2[5*S*-ODPY]$_4$
1c.61 R = $CONMe_2$ Rh_2[5*S*-DMAP]$_4$



1c.62 R = CO_2Me, X = H Rh_2[4*S*-MEOX]$_4$
1c.63 R = CO_2Me, X = Me Rh_2[4*S*-THREOX]$_4$
1c.64 R = Bn, X = H Rh_2[4*S*-BNOX]$_4$
1c.65 R = *i*-Pr, X = H Rh_2[4*S*-IPOX]$_4$
1c.66 R = Ph, X = H Rh_2[4*S*-PHOX]$_4$



1c.77 R = CO_2Me, X = Me Rh_2[4*S*-MACIM]$_4$
1c.78 R = CO_2Me, X = Ph Rh_2[4*S*-MBOIM]$_4$
1c.79 R = CO_2Me, X = 4-*t*-BuC_6H_4 Rh_2[4*S*-TBOIM]$_4$
1c.80 R = CO_2Me, X = Bn Rh_2[4*S*-MPAIM]$_4$
1c.81 R = CO_2Me, X = $PhCH_2CH_2$ Rh_2[4*S*-MPPIM]$_4$
1c.82 R = CO_2Me, X = *c*-$C_6H_{11}CH_2$ Rh_2[4*S*-MCHIM]$_4$

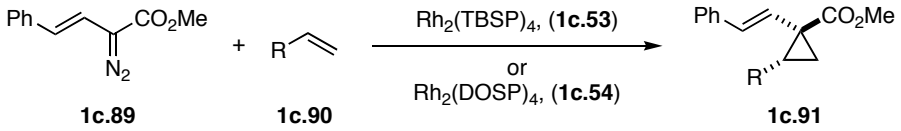


1c.83 R = *i*-Bu Rh_2[4*S*-IBAZ]$_4$
1c.84 R = Bn Rh_2[4*S*-BNAZ]$_4$
1c.85 R = Me Rh_2[4*S*-MEAZ]$_4$
1c.86 R = CH_2CMe_3 Rh_2[4*S*-IBAZ]$_4$
1c.87 R = *c*-C_6H_{11} Rh_2[4*S*-CHAZ]$_4$
1c.88 R = *l*-menthyl Rh_2[4*S*-, *R*-menthAZ]$_4$

Diazoesters substituted by an aryl or vinyl group were also explored as substrates in the enantioselective cyclopropanation reaction. These types of reagents are attractive in that they incorporate a second functional group to serve as a handle for future

manipulations. Early results indicated that rhodium(II) catalysts provided the best ratios of *trans*/*cis* isomers than most other transition metal catalysts.[197] Davies was the first to explore the use of auxiliaries on the diazoester substrate[198,199] and chiral dirhodium(II) catalyst for the asymmetric cyclopropanation of this class of compounds.[187] In 1996, Davies showed that the cyclopropanation of alkene **1c.90** with vinyldiazoester **1c.89** in the presence of either dirhodium(II) carboxylate catalysts **1c.53** or **1c.54** proceeded with an excellent level of enantiocontrol (Table 1c.1).[160] The yields were moderate at best, with the simple vinylacetate **1c.90** (R = OAc) substrate suffering from a particularly poor 26% yield (entry 2). Although complete diastereocontrol was observed in each case, *trans*-disubstituted alkenes were unreactive under the optimized conditions. Alternatively, chiral auxiliaries could be implemented in the transformation in lieu of a chiral dirhodium(II) catalyst. Excellent diastereoselectivity was observed in these reactions to provide a single diastereomeric product. The method was also quite efficient, producing the cyclopropanation products in good yields.[199]

Table 1c.1. Enantioselective rhodium(II)-catalyzed intermolecular cyclopropanation.

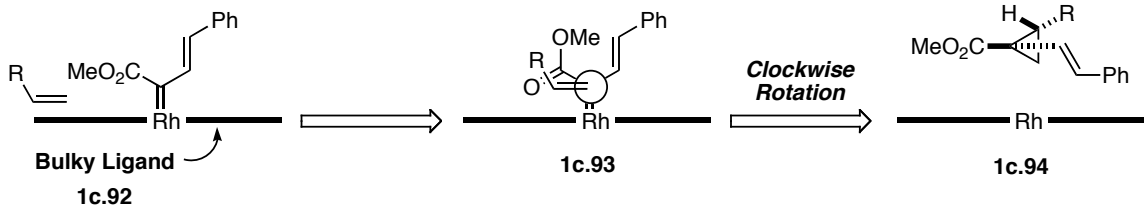


1c.89 **1c.90** **1c.91**

Entry	*R*	*Catalyst*	*Yield (%)*	*ee (%)*
1	Ph	**1c.54**	68	98
2	AcO	**1c.54**	26	95
3	EtO	**1c.54**	65	93
4	*i*-Pr	**1c.53**	58	95

To rationalize the level of diastereocontrol asymmetric induction observed in these chiral dirhodium(II)-catalyzed intermolecular cyclopropanations, the authors proposed a model as exemplified by Figure 1c.6.[160] Upon decomposition of the vinyldiazoester with the chiral rhodium catalyst, the resulting metallocarbene intermediate formed is depicted by structure **1c.92.** Approach of the alkene to the stabilized carbene center from the side of the electron-withdrawing group leads to structure **1c.93**. Clockwise rotation of the alkene during the cyclopropanation event yields the cyclopropane product **1c.94**. The unusually high level of diastereocontrol arises from the approach of the alkene in the metallocarbene intermediate from the side occupied by the ester functionality. The presence of both an electron-donating group, such as a vinyl moiety, and an electron-withdrawing group (*i.e.* methyl ester) is critical to controlling the approach of the alkene in this fashion. Substrates which lack this dual push-pull relationship of electron flow suffer from particularly low diastereocontrol with these dirhodium(II) catalysts as was observed with unsubstituted α-diazoesters.

Figure 1c.6. Model for stereocontrol observed in the dirhodium(II)-catalyzed cyclopropanations.

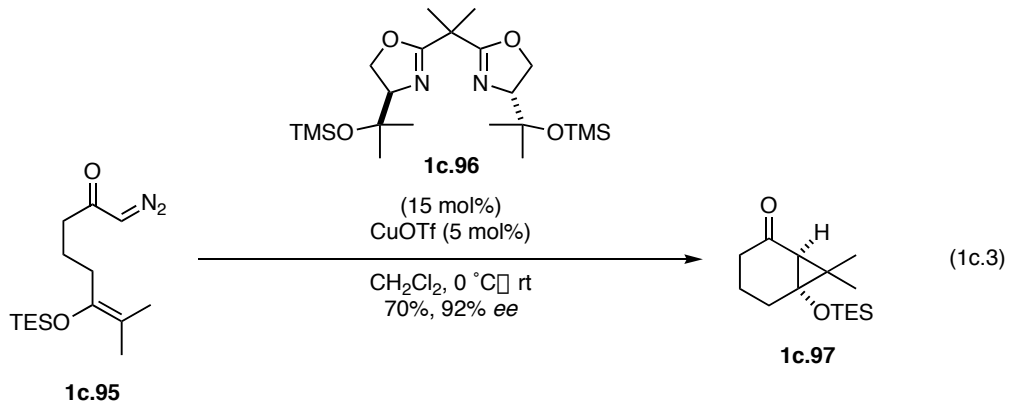


1.C.2 Intramolecular Cyclopropanations

Intramolecular cyclopropanations in which the diazoester functionality and the alkene to be cyclopropanated are tethered within the same molecule provide an opportunity to form various bicyclic ring systems.[200,201] The issue of diastereocontrol is

crucial, but in the formation of larger ring structures where the absence of steric strain allows for the formation of diastereomeric products stereocontrol can become more problematic. Typically, the most successful substrates have involved □,□-unsaturated or □,□-unsaturated diazocarbonyl systems to form [3.1.0] and [4.1.0] bicyclic products. In these cases, diastereocontrol is not an issue because only one diastereomer can be formed due to the inherent ring strain of the bicycle. Although a number of different transition metals are capable of catalyzing these transformations, copper and rhodium catalysts have been found to be particularly successful at inducing exceptional enantioselectivity. Additionally, the types of substrates that can be used for this reaction class can be categorized into three classes, diazoketones, diazoesters and diazoacetamides. Each type of substrate has been shown to be suitable in asymmetric intramolecular cyclopropanations.

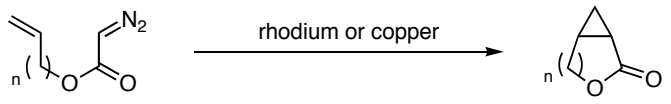
The use of chiral catalysts for mediating the intramolecular cyclopropanation of diazoketones has been thoroughly examined, and until recently, Pfaltz obtained the best results with the copper(I) catalyst **1c.40.**[202] Although good to excellent enantioselectivities were observed, the reactions typically suffered from low yields (<60%). Since then a number of dirhodium(II) catalysts derived from ortho-metallated aryl phosphine ligands exhibited excellent yields and comparable enantioselectivities.[203] However, the copper(I) derived species seem to be the preferred transition metal complexes for catalyzing this class of transformations. In his phorbol CD-ring skeleton synthesis, Shibasaki showed that the asymmetric copper(I)-catalyzed cyclopropanation could be performed on a silyl enol ether. When silyl enol ether **1c.95** was treated with the bis(oxazoline) catalyst **1c.96**, the desired [4.1b.0] bicycle **1c.97** was produced in good yield (70%) and 92% *ee* (Eq. 1c.3).[204,205]



(1c.3)

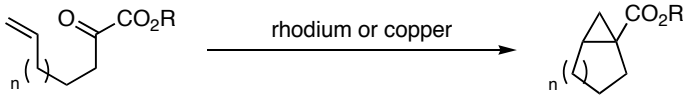
The intramolecular cyclopropanation of diazoacetates constitutes an important class of substrates. This reaction has found a number of useful applications in target oriented synthesis as a method for the formation of [*n*.1.0] bicycles. Depending upon the nature of the diazoacetate substrate employed, the products obtained from this transformation can be divided into two categories. The most common cyclopropane products, the *Class A* cyclopropyl lactone **1c.99**, is derived from a substrate in which the pendant olefin is incorporated into the ester **1c.98** (Eq. 1c.4). The second category, *Class B*, is not quite as common due to the fewer synthetic opportunities their products present. The substrates typified by this category incorporate the alkene into part of the alkyl side chain of the molecule, as depicted by **1c.100** (Eq. 1c.5). The products arising from these cyclopropanations are cyclopropanecarboxylates **1c.101.** This reaction is far less common, and suffers from the lack of a chiral catalyst which can render this reaction asymmetric with synthetically useful selectivities.[206]

Class A: Cyclopropyllactone Formation



1c.98 **1c.99** (1c.4)

Class B: Cyclopropanecarboxylate Formation

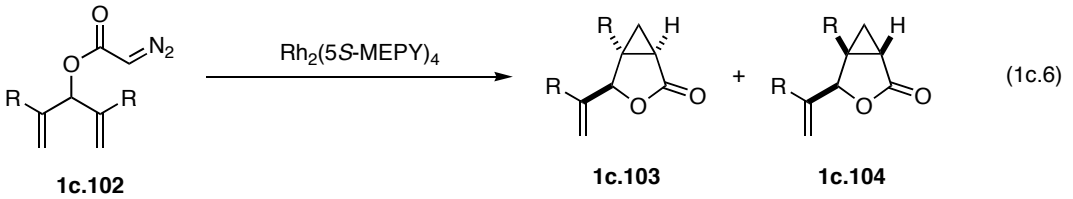


1c.100 **1c.101** (1c.5)

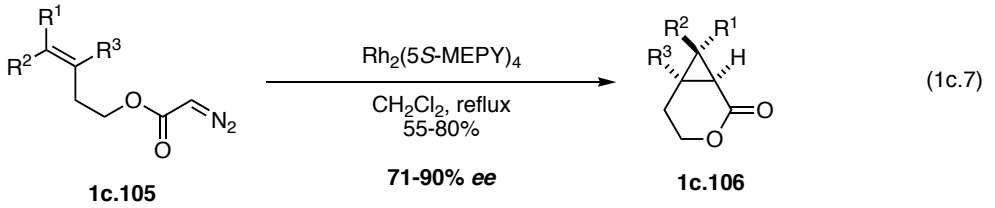
Small (five and six membered) and medium/large rings are accessible from the *Class A* cyclopropanations. The dirhodium(II) carboxamidate catalysts are optimal in the asymmetric synthesis of small ring bicyclic lactones, whereas medium/large ring products are formed with superior enantiocontrol by using the bis(oxazoline) ligated copper(I) species.[207] A number of other catalysts have also shown utility in the intramolecular asymmetric cyclopropanation of diazoesters including cobalt[208] and ruthenium.[209] These metals have been shown to be particularly useful in the synthesis of trisubstituted cyclopropanes in the formation of small ring bicycles

The synthesis of 1,2,3-trisubstituted cyclopropanes has also been a compelling area of study in intramolecular cyclopropanations. If the diazoacetate is secondary or tertiary the issue of endo versus exo diastereomers arises, thereby complicating issues of diastereoselectivity. The chiral dirhodium(II) carboxamide catalyst Rh_2[(5*S*)-MEPY]$_4$ has been shown to impart exemplary enantiocontrol, and in some cases diastereocontrol, in the cyclopropanation of these substrates. In 1994, Martin and coworkers illustrated that divinyl diazoesters **1c.102** underwent cyclopropanation in the presence of Rh_2[(5*S*)-MEPY]$_4$ to yield cyclopropyl lactones **1c.103** and **1c.104** in good yields and

enantioselectivities (Eq. 1c.6).[210] In the case of monosubstituted (R = H) divinyl substrates, the diastereoselectivity observed was excellent (**1c.103/1c.104** > 95:5). However, when the olefins were symmetrically 1,2-disubstited (R = Me), the two diastereomers were formed in nearly equal amounts. Homoallylic diazoacetates **1c.105** were also viable cyclopropanation substrates with Rh_2[(5*S*)-MEPY]$_4$ to form the corresponding [4.3.0] bicycles **1c.106** in moderate yields and with slightly lower enantioselectivities overall (Eq. 1c.7).[194,211] One observation made by the authors was that the olefin substitution was not critical in dictating the stereochemical outcome of the cyclopropanation of diazoacetate **1c.105** as it was for the corresponding allylic diazoacetates **1c.102**.

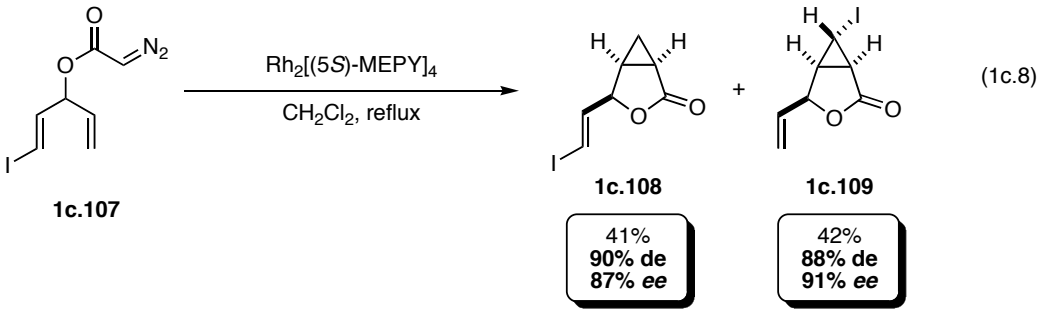


R = H	75%	>95 (≥94% *ee*)	<95
R = Me	73%	45 (92% *ee*)	55 (91% *ee*)



In addition to analyzing the diastereoselectivity of 1,1-disubstituted divinyl diazoesters such as **1c.102**, the Martin group also examined how the corresponding 1,2-disubstituted substrates, such as vinyl iodide **1c.107**, would react under standard

cyclopropanation conditions. It was discovered that upon diazodecomposition of **1c.107** with Rh_2[(5*S*)-MEPY]$_4$, regioisomers **1c.108** and **1c.109** were formed in excellent diastereomeric ratios and enantioselectivities.[210] In this way, racemic divinyl diazoacetates could be kinetically resolved by formation of the corresponding cyclopropyl lactones selectively. Intriguingly, the chiral catalyst was capable of selectively cyclopropanating one enantiomer of diazoacetate **1c.107** onto both pendant olefins thereby forming the two regioisomers, enantioselectively. This reaction represents one of the early examples of parallel kinetic resolution.



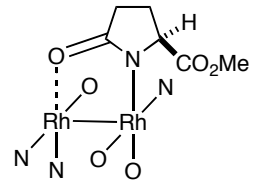
(1c.8)

1.C.2.3 The Origin of Diastereo- and Enantioselection in the Intramolecular Asymmetric Cyclopropanation of α-Diazoesters with Chiral Rhodium(II) Catalysts

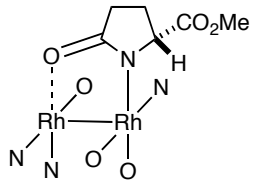
Although a number of chiral dirhodium(II) carboxamidate catalysts have found utility in the intramolecular asymmetric cyclopropanation reaction, a great majority of the work in exploring the chemo-, diastereo-, and enantioselectivities associated with this class of chiral catalysts have been performed utilizing the 5-MEPY **1c.58a/b** dirhodium(II) series (Figure 1c.7).[126] The carboxamide ligands orient themselves around the metal center as illustrated by structures **1c.58a** and **1c.58b**, a trend followed by the majority of carboxamide ligands associated with the dirhodium(II) cyclopropanation

catalysts.[171] As alluded to earlier, this leaves the axial coordination sites on the metal open for carbene formation. When viewed along the Rh-C bond of the metal-stabilized carbene, the face of the catalyst can be divided into four quadrants in which the substrate approach can occur. Two of these quadrants are occupied by the methyl carboxylate group on the ligands themselves leaving only one open for the carboxylate group of the substrate and the other for approach of the alkene. Calculations have shown that the preferred spatial arrangement is that dictated by structure **1c.111** in which the olefin approaches the electrophilic carbene center from the less hindered *si* face. Structure **1c.110** where the olefin approaches the carbene center by bisecting the N-Rh-N bond angle has a higher calculated energy minima, and it is therefore postulated that it contributes less to the overall product distribution.

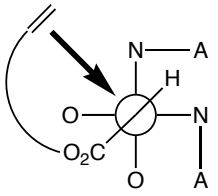
Figure 1c.7. Structures and proposed substrate approach in the $Rh_2[5(S)\text{-MEPY}]_4$-$Rh_2[5(R)\text{-MEPY}]_4$-catalyzed cyclopropanations



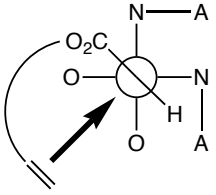
$Rh_2(5S\text{-MEPY})_4$ (**1c.58a**)



$Rh_2(5R\text{-MEPY})_4$ (**1c.58b**)



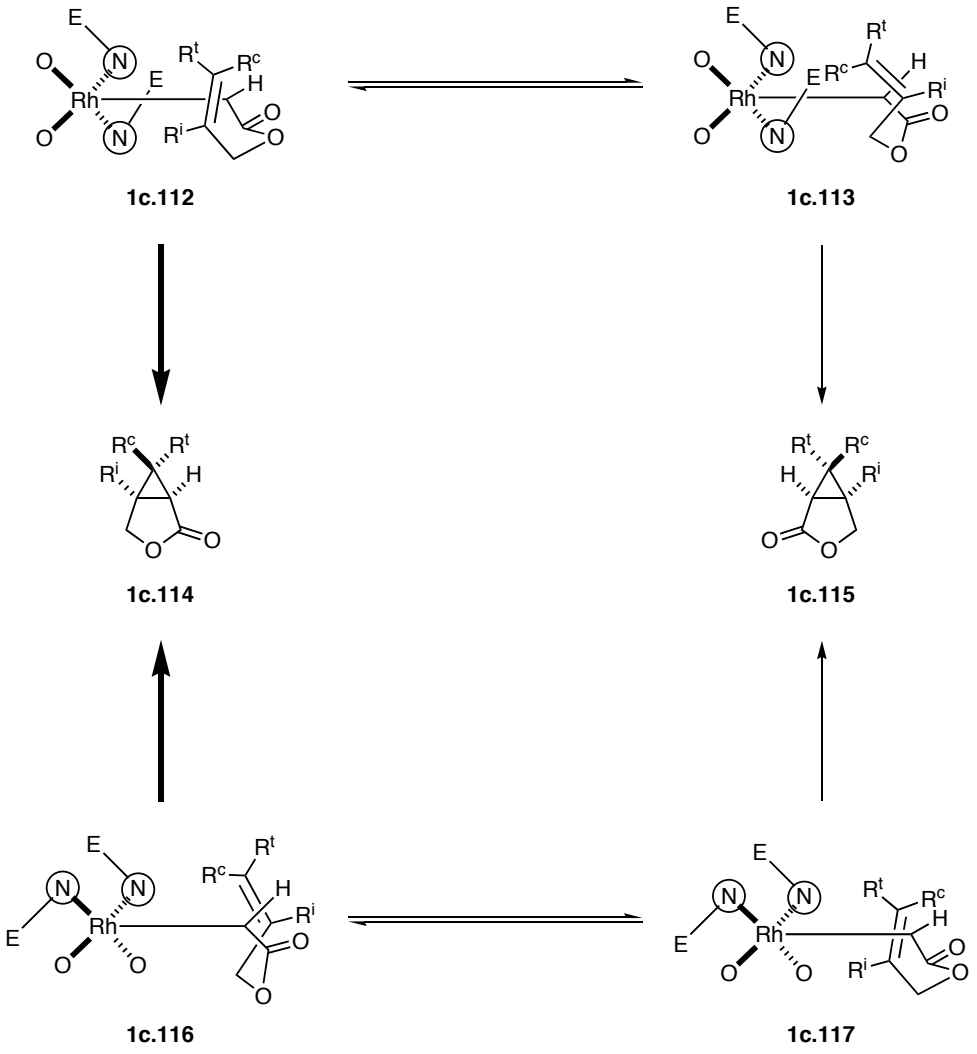
1c.110



1c.111

A simple model to explain the observed enantioselectivities obtained by using Rh_2[(5*R*)-MEPY]$_4$ is illustrated below in Scheme 1c.6.[191] Considering the approach angle of the olefin, which was calculated to have the lowest possible energy minima in structure **1c.111**, the steric limitations on the metal stabilized carbene dictate that the orientation, when R^i = H, is represented by **1c.112.** Upon cyclopropanation, structure **1c.112** produces the observed cyclopropane product **1c.114**, whereas the rotameric **1c.113** provides the minor enantiomeric adduct **1c.115**. Alternatively, if angle of approach in the higher energy structure **1c.116** is considered, the reaction proceeds to form the enantiomeric cyclopropanes **1b.114** and **1c.115** *via* the rotameric structures **1c.116** and **1c.117**. Analysis of structure **1c.112**, which leads to the observed major product, shows that a *trans* substituent (R^t) would interact unfavorably with the ester functionality on the carboxamidate ligands thereby leading to a decrease in the energy difference between **1c.112** and **1c.113**. This decrease in energy would cause a decrease in the enantioselectivities, which is in fact what is observed. However, the presence of a *cis* substituent (R^c) should not adversely effect the outcome of the reaction due to the remote position of R^c to the reacting center. Their hypothesis is likewise supported by the experimental data.

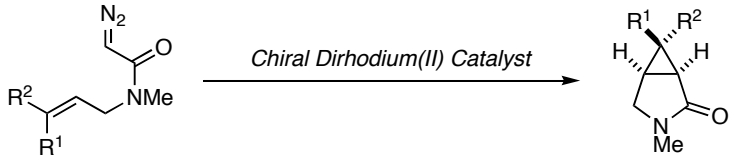
Scheme 1c.6



Diazoacetamides were also analyzed for their efficacy in the intramolecular cyclopropanation reaction.[212] As illustrated in Table 1c.2, Rh_2[(5*S*)-MEPY]$_4$ provided superior results for diazoacetamide **1c.118** (compare entries 1 and 2) in which the olefin was monosubstituted.[213] However, the presence of a methyl group at the terminus of the olefin required the use of Rh_2[(4*S*)-MPPIM]$_4$ to provide a good yield and enantioselectivity. It is noteworthy that the use of *N*-methyl acetamides as

cyclopropanation substrates resulted in minimal dipolar addition side-products, and provided the s-*trans* conformers preferentially.

Table 1c.2. Enantioselective intramolecular cyclopropanation of diazoacetamide **1c.118**.



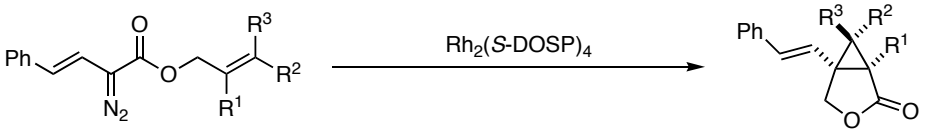
1c.118 **1c.119**

Entry	*R*[1]	*R*[2]	*Catalyst*	*Yield (%)*	*ee (%)*
1	H	H	Rh_2[(5*S*)-MEPY]$_4$	62	93
2	H	H	Rh_2[(4*S*)-MPPIM]$_4$	20	75
3	Me	Me	Rh_2[(4*S*)-MPPIM]$_4$	88	94

The use of aryl and vinyl diazoacetates in the enantioselective intramolecular cyclopropanation proved to be a more challenging endeavor than their corresponding alkyl counterparts. For these substrates, a more reactive catalyst was required. Consequently, a delicate balancing act ensued to establish conditions that provided the best yield and optimal enantioselectivity. Davies has shown that the chiral dirhodium(II) catalyst, Rh_2[(*S*)-DOSP]$_4$ (**1c.54**), is quite useful in catalyzing these stubborn cyclopropanations in an asymmetric fashion.[159] When vinyl diazoester **1c.120**, containing either a 1,1- or trisubstituted, was treated with **1c.54**, the corresponding cyclopropane **1c.121** was obtained in moderate yield and good enantioselectivity (entries 2 and 3, Table 1c.3). However, when a monosubstituted olefin was employed, the yield of the

transformation was good (81%) although the enantioselectivity suffered (28% *ee*) (entry 1).

Table 1c.3. Asymmetric intramolecular cyclopropanation of vinyl diazoacetate **1c.120**.

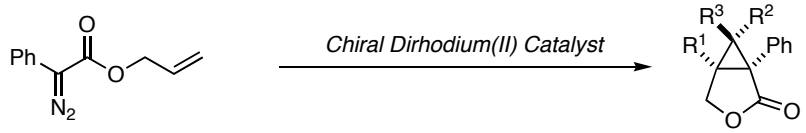


1c.120 **1c.121**

Entry	*R¹*	*R²*	*R³*	*Yield (%)*	*ee (%)*
1	H	H	H	81	28
2	Me	H	H	53	87
3	Me	Me	Me	46	60

Doyle has recently shown that the use of aryl diazoacetates provides the corresponding cyclopropyl lactones in excellent yield and enantioselectivity when the dirhodium(II) species Rh_2[(4*S*)-IBAZ]$_4$ (**1c.83**) and Rh_2[(4*S*)-MEAZ]$_4$ (**1c.85**) are employed (Table 1c.4).[196,214,215] Treatment of aryl diazoester **1c.122** with **1c.54** resulted in an excellent yield (92%), but poor enantiomeric excess (28% *ee*) (entry 1). However, utilizing Doyle's chiral dirhodium(II) carboxamidate catalysts **1c.83** and **1c.85**, the desired products were obtained in good yield (≥ 80%) and moderate enantiomeric excess (≥ 68% *ee*).

Table 1c.4. Asymmetric intramolecular cyclopropanation of aryl diazoacetate **1c.122.**



1c.122 **1c.123**

Entry	*Catalyst*	*Yield (%)*	*ee (%)*
1	Rh_2[(*S*)-DOSP]$_4$	92	28
2	Rh_2[(4*S*)-IBAZ]$_4$	83	64
3	Rh_2[(4*S*)-MEAZ]$_4$	80	68

1.C.3 The Transition Metal-Catalyzed [5+2] Cycloaddition of Alkynes and Vinyl Cyclopropanes

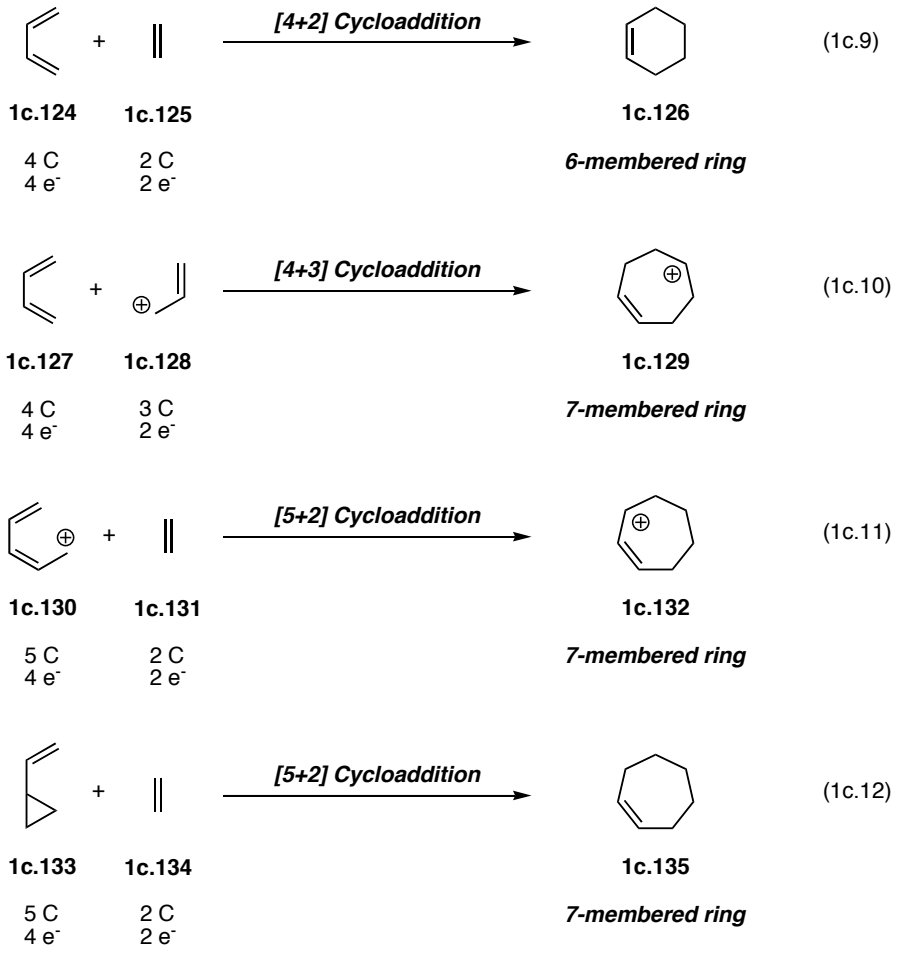
Although a long standing goal in the synthetic community has been to develop efficient, atom economical methods to assemble complex molecules, in recent years, greater emphasis has been placed on synthetic routes which exemplify these aspects. One focus of many synthetic methods is to create a way in which intermediates can be obtained in an environmentally friendly, practical and efficient manner. Cycloadditions constitute one of the most powerful ways in which the target compound can be efficiently synthesized, as these reactions often allow for the formation of multiple bonds and the creation of a number of stereocenters in a one-pot sequence. Another requirement, which most cycloadditions adeptly fulfill, is the use of readily available starting materials.[216] Possibly the most often utilized cycloaddition reaction is the Diels-Alder cycloaddition.[217] The desire to form six membered rings in a concise, stereocontrolled manner has kept the Diels-Alder reaction at the forefront of modern organic synthesis. The simple

requirement of a diene and dienophile, formally a 4π electron system in conjunction with a 2π electron system, make the Diels-Alder reaction that much more attractive (Eq. 1c.9).

The available methods for seven-membered ring synthesis are much less general than the Diels-Alder reaction in that they are often severely limited in scope. The number of ways in which one can construct a seven-membered ring are few in comparison to the wide range of methods for the synthesis of their six-membered analogs. The two basic methods of assembling seven-membered rings are essentially isoelectronic variations of each other. The first involves exchanging the dienophile 2π electron component in the Diels-Alder reaction for a 3 carbon, 2π electron allyl cation fragment **1c.128**, as illustrated in Eq. 1c.11a. Such [4+3] cycloadditions yield the cationic 7-membered ring **1c.129**.[218-220] The second variant employs a pentadienyl cation **1c.130** which can then undergo a charged [5+2] cycloaddition to yield the allyl cationic seven-membered ring **1c.132** as illustrated in Eq. 1c.11b.[221-223] Unfortunately, both methods described require the use, or formation of ionic intermediates to achieve the desired carbon-carbon bond forming events.

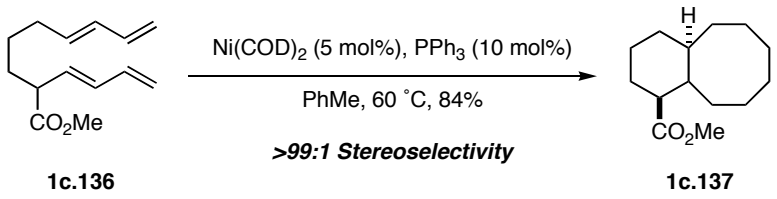
A unique solution to the issue of ionic intermediate involvement was first posed by Sarel and Breuer in 1959.[224] The authors proposed that the reactivity pattern shared by vinylcyclopropanes and dienes could be harnessed to yield seven-membered rings *via* a cycloaddition pathway. Their hypothesis was such that the reaction of an electronically neutral vinylcyclopropane (5 carbon, 4 electron component), in place of the diene component in the Diels-Alder reaction, with a dienophile (2 carbon, 2 electron component) would yield the corresponding seven-membered ring by a concerted cycloaddition/cyclopropyl ring opening pathway (Eq. 1c.12). They reported that a phenyl substituted vinylcyclopropane reacted with maleic anhydride to yield a seven-membered ring product through a [5+2] cycloaddition pathway. Unfortunately, repeated attempts by

independent research groups to reproduce this result proved fruitless.[225] In some isolated examples, vinylcyclopropanes were shown to react with activated olefins, but only to yield products arising from the [2+2] cycloaddition pathway.[226]



Although numerous attempts were made, a useful [5+2] cycloaddition strategy had proved elusive. A few reports had surfaced in which the authors were able to obtain products containing seven-membered rings, but the methods were extremely limited in scope, and the vinylcyclopropanes involved required activation by enhanced ring strain associated with incorporation into a heteroatom-containing bicyclic array.[227-229]

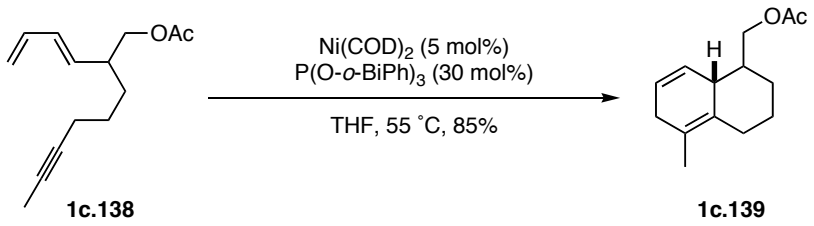
Fortunately, the 1980's saw this problem of medium ring synthesis addressed in a bold new way, namely through the use of transition metal catalysis.[145] A number of research groups began by examining the use of transition metals to catalyze those reactions which proved difficult or impossible through the use of conventional synthetic methods. Notably, Wender and coworkers reported in 1986 the first example of a transition metal-catalyzed intramolecular [4+4] cycloaddition of *bis*-dienes to yield eight-membered rings.[230] The overall reaction process is thermally forbidden and even under photochemical conditions is inefficient, often leading to the more entropically favored [2+2] cycloadduct. However, as illustrated in Eq. 1c.14, treatment of diene **1c.136** with the metal complex $Ni(COD)_2$ and PPh_3 provided the [4+4] cycloadduct **1c.137** in 84% yield and with excellent stereoselectivity (>99:1). The process proved to be quite broad in scope as a wide array of substrates were tolerated, thereby allowing access to the core carbon frameworks of a variety of natural products.



1c.136 **1c.137** (1c.13)

In addition to catalyzing [4+4] cycloadditions, otherwise difficult [4+2] cycloadditions have also been reported as proceeding smoothly in the presence of transition metal complexes. For example, diene **1c.138** suffers from decomposition under standard Diels-Alder conditions. However, in the presence of a nickel(0) catalyst, the dienyne readily undergoes the metal-catalyzed [4+2] cycloaddition to provide 1,4-diene **1c.139** (Eq. 1c.14).[231] Given the success at constructing six- and eight-membered rings

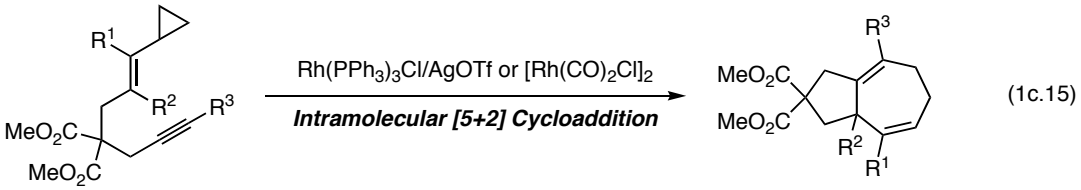
through the use of transition metal catalysts, efforts were turned toward the assembly of seven-membered ring products.



(1c.14)

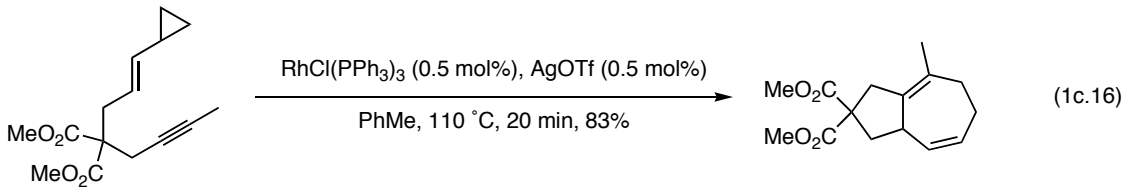
1.C.3.1 The First Transition Metal-Catalyzed Intramolecular [5+2] Cycloadditions

In 1995, Wender an coworkers reported the use of a transition metal catalyst to construct seven-membered rings through a formal intramolecular [5+2] cycloaddition strategy.[232] When vinylcyclopropylenynes **1c.140** were treated with a rhodium(I) catalyst, the [5.3.0] bicycles **1c.141** were be obtained (Eq. 1c.15). The process proved to be exceptionally efficient and broad in scope, thereby providing a long awaited solution to the problem of medium-sized ring construction. The process has been shown to be suitable for a variety of substituted *E*- and *Z*-alkenes.[233] Additionally, electron rich, electron poor and conjugated internal and terminal alkynes were fitting substrates.[234] Systems with additional substitution on the alkene moiety proved efficient [5+2] cycloaddition precursors, providing the desired cycloadducts under the optimized conditions. For some sterically congested substrates with multiple substituents along the 1,6-enyne backbone (R^1, $R^2 \neq H$), longer reaction times were required to achieve complete consumption of the starting enyne. Yields for the transformation were found to be quite insensitive to reaction concentration, but concentrations of 0.05 to 0.1 were found to be optimal. Reactions run at concentrations above 1a.1 become heterogeneous and were slower, although they still proceeded in good yield.[235]



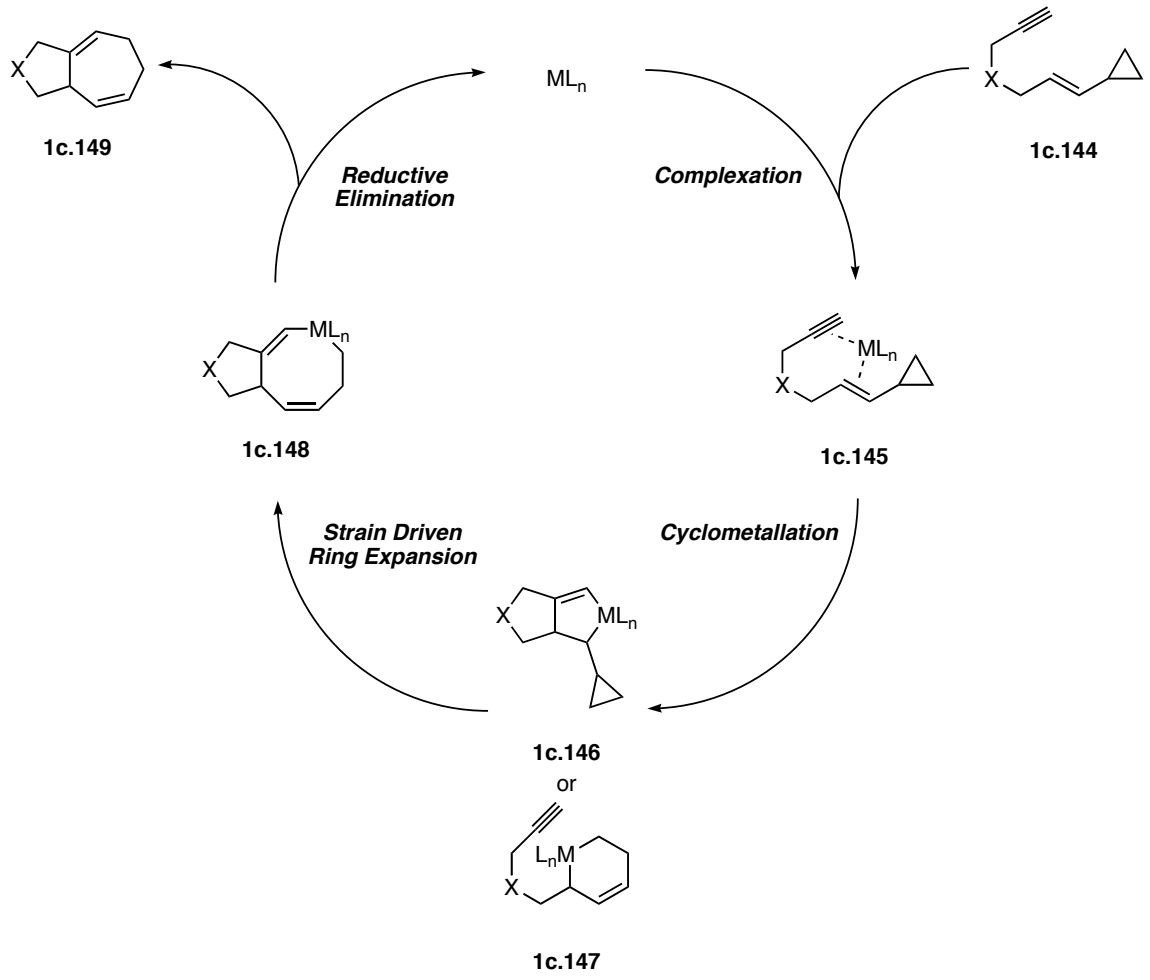
1c.140 **1c.141** (1c.15)

When vinylcyclopropane **1c.142** was treated with 10 mol% $RhCl(PPh_3)_3$ in PhMe, cycloadduct **1c.143** was obtained in 84% yield after 48 h.[232] However, increasing the solvent polarity by using trifluoroethanol in place of PhMe, allowed the reaction to reach completion in only 19 h. The authors propose that this dramatic decrease in reaction time is due to facilitated ligand dissociation commonly experienced with solvents of increased polarity. Remarkably, when 0.5 mol% of $RhCl(PPh_3)_3$ was used in conjunction with 0.5 mol% AgOTf in PhMe at 110 ˚C, the desired cycloadduct **1c.143** was obtained in 83% yield after 20 min (Eq. 1c.16). The addition of AgOTf to the reaction mixture is thought to facilitate the irreversible formation of a vacant coordination site on the rhodium(I) species by precipitating AgCl from the solution. This seminal work by Wender's group proved to be the beginning of an elaborate study toward illustrating the impact the rhodium(I)-catalyzed [5+2] cycloaddition would be to modern synthetic chemistry.



1c.142 **1c.143** (1c.16)

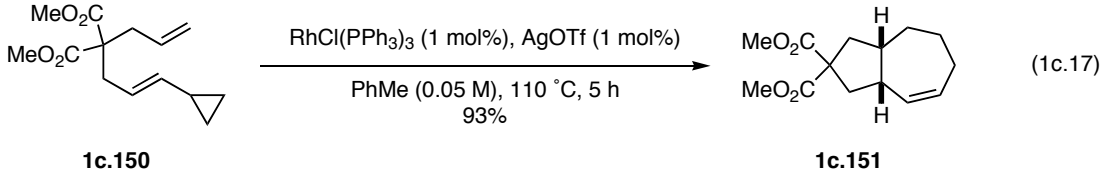
Scheme 1c.7



The mechanistic design behind the development of this transition metal-catalyzed [5+2] cycloaddition is illustrated in Scheme 1c.7.[236] Initial complexation of the metal species to cyclopropyl enyne **1c.144** provides intermediate **1c.145**. Subsequent oxidative addition to the enyne moiety *via* a well established cyclometallation pathway yields either the five- or six-membered metallocycles **1c.146** or **1c.147** respectively. Assisted strain driven ring expansion of the cyclopropane by the proximal metal-carbon bond occurs to yield metallocyclooctadiene **1c.148**. Reductive elimination of the transition metal

catalyst regenerates the active complex and provides the [5+2] cycloadduct **1c.149**. Overall, the ingenuity and foresight exhibited by the Wender group resulted in the first catalytic [5+2] cycloaddition reaction of a vinylcyclopropane and alkyne.

The method was further extended to include the intramolecular [5+2] cycloaddition of cyclopropyl dienes of the type **1c.150** (Eq. 1c.17).[233] The use of 1,6-dienes in this metal-catalyzed reaction provided the first insight into the relative stereochemistry at the bridgehead carbon atoms. Additionally, utilizing alkenes in the place of alkynes allowed access into previously difficult seven-membered ring analogs which can be utilized as intermediates in target directed synthesis. Therefore, treatment of ene-vinylcyclopropane **1c.150** with 1 mol% $RhCl(PPh_3)_3$ and 1 mol% AgOTf provided cycloadducts **1c.151** in 93% yield as a *single* diastereomer.



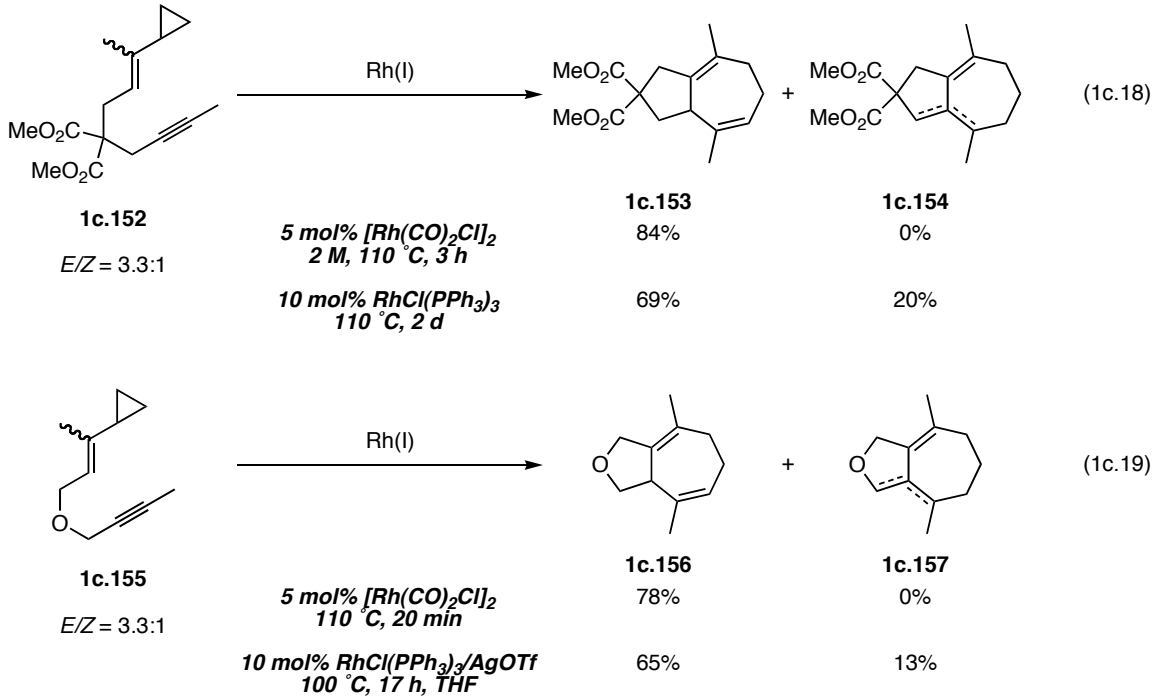
1c.150 **1c.151** (1c.17)

1.C.3.2 Regio- and Stereoselectivity in the Rhodium(I)-Catalyzed Intramolecular [5+2] Cycloaddition of Cyclopropyl Enynes

In 1998, Wender and coworkers reported the use of a new rhodium(I) species capable of catalyzing the [5+2] cycloaddition in a uniquely selective fashion.[234] They found that $[Rh(CO)_2Cl]_2$ catalyzed the intramolecular [5+2] cycloaddition of various cyclopropylenynes to typically provide the [5.3.0] bicyclic cycloadducts in a more efficient fashion than the analogous $RhCl(PPh_3)_3$/AgOTf catalyzed reactions. This observation led to a detailed analysis of the scope and utility of this novel [5+2]

cycloaddition catalyst. In multiple instances the $RhCl(PPh_3)_3$/AgOTf catalyst system either failed to provide the desired cycloadduct, proceeded in low yield after extended reaction times at elevated temperatures, or gave mixtures of double bond isomers in the products with a number of different substrates. Wender thus discovered a new catalyst that would prove more efficient at catalyzing the cycloaddition of problematic substrates.

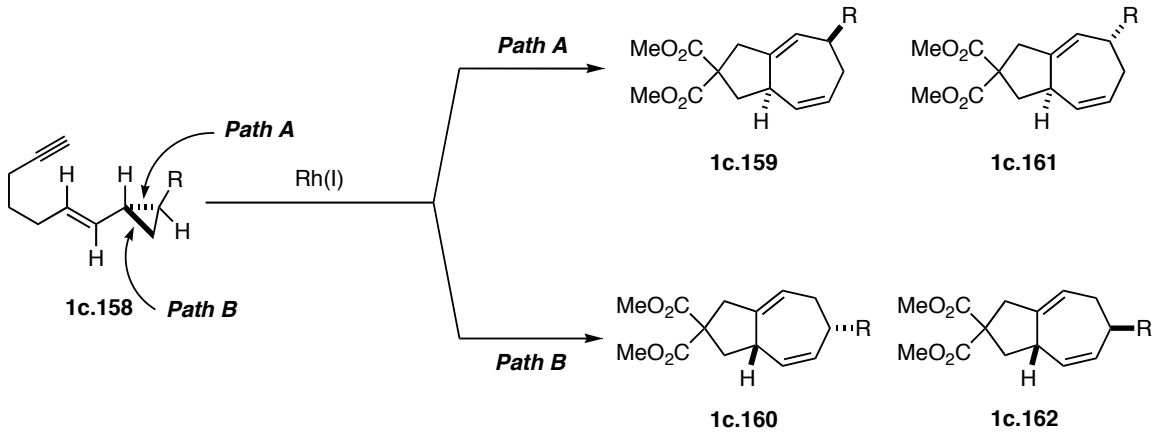
When $[Rh(CO)_2Cl]_2$ was used as the rhodium(I) source to catalyze the [5+2] cycloaddition of cyclopropylenynes **1c.152** and **1c.155**, cycloadducts **1c.153** and **1c.156** were obtained in excellent yields without formation of the double bond isomerized byproducts **1c.154** and **1c.157** (Eqs. 1c.18 and 1c.19). However, when $RhCl(PPh_3)_3$ was used to catalyze the reaction of enyne **1c.152**, cycloadduct **1c.153** was obtained in a diminished 69% yield after 2 d along with 20% of the double bond isomers **1c.154**. Likewise, when enyne **1c.155** was treated with $RhCl(PPh_3)_3$/AgOTf at 100 °C for 17 h, a mixture (5:1) of cycloadducts **1c.156** and **1c.157** was produced. The authors propose that the lower ligand count of the anticipated active catalyst species, $Rh(CO)_2Cl$, may aid in cyclopropane ring expansion by facilitating coordination to the metal. Unfortunately, when the dimeric rhodium(I) catalyst, $[Rh(CO)_2Cl]_2$, was used to facilitate the cycloaddition of enynes containing terminal alkynes and alkenes, no cycloadducts were obtained. However, the $RhCl(PPh_3)_3$/AgOTf combination gave moderate to high yields of the desired products. As for those cases in which a terminal alkyne was involved, the authors proposed that the electron deficient nature of the catalyst led to primarily alkyne C-H insertion over the [5+2] cycloaddition pathway. With regards to the presence of a terminal alkene, no reaction occurred even after prolonged reaction times at elevated temperatures.



A systematic study was performed by Wender and coworkers in 1999 to analyze the regio- and stereochemical trends observed in the $[Rh(CO)_2Cl]_2$-catalyzed [5+2] cycloaddition.[237] The results seemed to indicate that the stereoselectivity in the reaction is independent of the rhodium(I) catalyst. However, the regioselectivity observed when disubstituted cyclopropanes were employed as substrates varied markedly on the source of rhodium(I) and the nature of the functional group substituent on the three-membered ring. Then, the [5+2] cycloaddition of a cyclopropyl enyne **1c.158** could potentially yield any one of the four possible regio- and diastereoisomers **1c.159-1c.162** (Scheme 1c.8). The diastereoselectivity in the cycloaddition was determined to depend solely on the stereochemistry around the cyclopropane ring. Enynes with *trans* substitution as in **1c.158** provide [5.3.0] bicycles with the proton at the bridgehead position and the substituent R in a *trans* alignment across the ring system as in cycloadducts **1c.159** and **1c.160**. However, enynes containing *cis*-cyclopropanes yield cycloadducts with the

corresponding relative stereochemistry in a *cis* configuration as depicted by structures **1c.161** and **1c.162**.

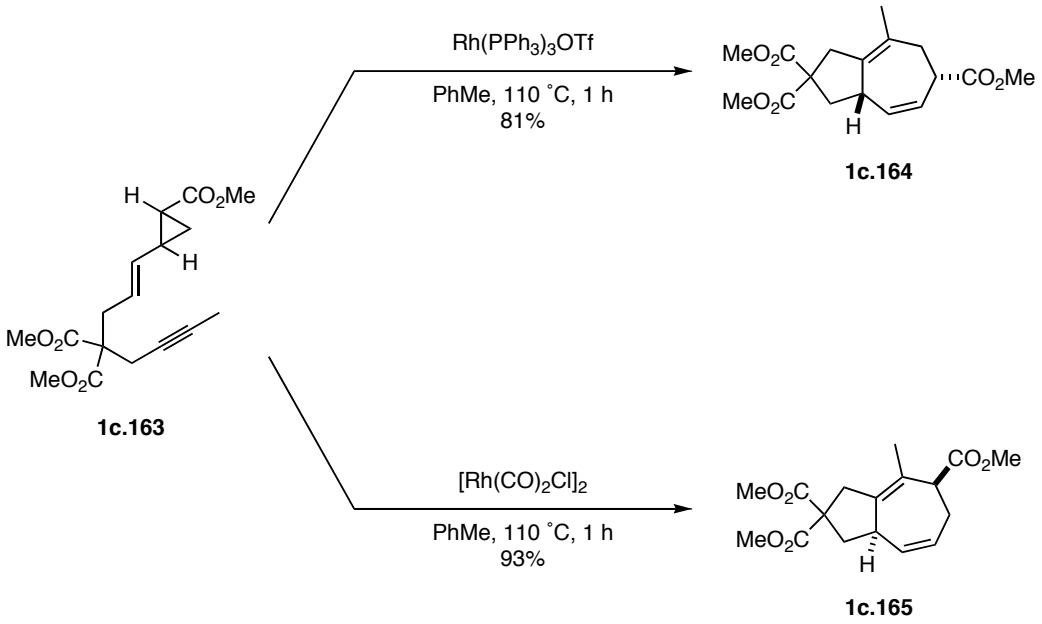
Scheme 1c.8



The regioselectivity in the intramolecular [5+2] cycloaddition reaction was not such a clear-cut issue. A number of factors seem to dictate whether the cycloaddition would proceed *via* Path A or Path B to yield either regioisomers **1c.159/1c.161** or **1c.160/1c.162**. The experimental results led the authors to propose that the regiochemical outcome of the reaction is determined by which bond of the cyclopropane is cleaved in the ring expansion step in the proposed mechanism outlined in Scheme 1c.8. If the more substituted cyclopropane bond is severed (Scheme 1c.8, path A) cycloadducts **1c.159** and **1c.161** are produced. However, if the less substituted bond is cleaved, the cycloaddition yields **1c.160** and **1c.162** following reductive elimination of the metal complex. It was determined that there existed a delicate balance of three separate factors dictating which regioisomer would be formed preferentially. First, the nature of the catalyst played a significant role in the regioselectivity, most notably in the *trans* series of cyclopropyl enynes. When methyl ester-substituted cyclopropanes such as **1c.163** were treated with $[Rh(CO)_2Cl]_2$, only one regioisomer **1c.165** was produced, whereas the

combination $RhCl(PPh_3)_3$/AgOTf provided the regioisomeric cycloadduct **1c.164** (Scheme 1c.9). Secondly, the functional group nature of the cyclopropane substituent strongly influenced the regioselectivity of the reaction. Functional groups varying from silyl-protected methyl carbinols to aldehydes and methyl esters often times gave very different results. Lastly, the stereochemistry about the cyclopropane ring also had an effect on the regiocontrol of the [5+2] cycloaddition, although not nearly as pronounced as the influence this factor had on the diastereoselectivity.

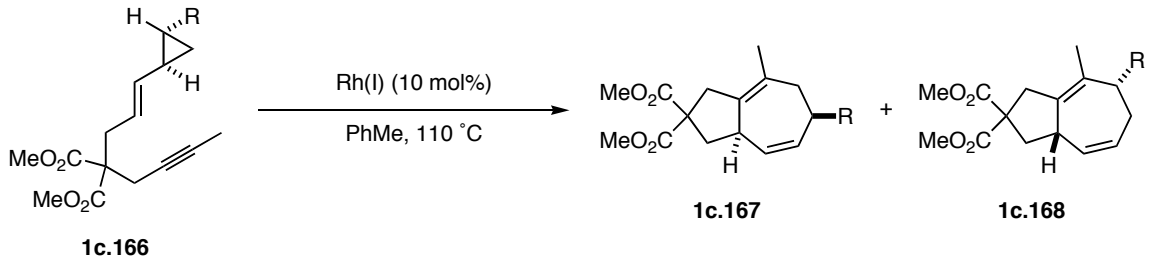
Scheme 1c.9



The *trans*-cyclopropylenyne **1c.166** was analyzed first to see how dramatic an effect the first two factors would play on the outcome of the cycloaddition (Table 1c.5). The substrates **1c.166**, in which the R group was either a silyl-protected carbinol or a methyl ester, gave good yields and exhibited excellent regiocontrol with $RhCl(PPh_3)_3$/AgOTf as the rhodium(I) source (entries 1 and 5). However, when an aldehyde functionality was present on the cyclopropane ring, this cationic rhodium

complex failed completely, giving only decomposition products. When $[Rh(CO)_2Cl]_2$ was employed as the cycloaddition catalyst, a different set of results was obtained for each enyne substrate. Excellent yields were obtained as was observed with $RhCl(PPh_3)_3$/AgOTf. However, the formyl substituted substrate proceeded in 98% yield, a result which contrasted sharply with the decomposition observed when $RhCl(PPh_3)_3$/AgOTf was employed. Additionally, the formyl substituted enyne proceeded with complete regioselectivity to provide exclusively cycloadduct **1c.168**. For R = CO_2Me, the regioselectivity was reversed, yielding a mixture (11:1) of cycloadducts favoring cleavage of the more substituted cyclopropane bond. When enyne **1c.166** (R = CH_2OTBS) was subjected to the optimized reaction conditions, the major cycloadduct was still **1c.167** regardless of the rhodium catalyst, but the level of regiocontrol was greatly diminished when $[Rh(CO)_2Cl]_2$ was used, decreasing from 100% to 77% of the product mixture.

Table 1c.5. The [5+2] cycloaddition of *trans*-2-substituted-1-vinylcyclopropanes.



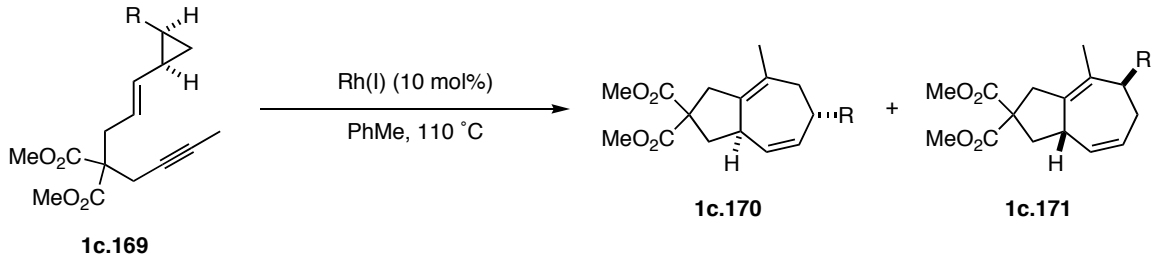
1c.166 **1c.167** **1c.168**

Entry	*R*	*Catalyst*	*Yield (%)*	*1c.167:1c.168*
1	CH_2OTBS	$Rh(PPh_3)_3OTf$	95	1:0
2	CH_2OTBS	$[Rh(CO)_2Cl]_2$	86	3.5:1
3	CHO	$Rh(PPh_3)_3OTf$	decomposition	-
4	CHO	$[Rh(CO)_2Cl]_2$	98	0:1
5	CO_2Me	$Rh(PPh_3)_3OTf$	81	20:1
6	CO_2Me	$[Rh(CO)_2Cl]_2$	93	1:11

The *cis*-cyclopropylenyne series produced noticeably different results than those observed for the corresponding *trans*-substrates. When cyclopropyl enyne **1c.169** was treated with $RhCl(PPh_3)_3$/AgOTf for each of the same functional groups that **1c.166** was tested with, similar regiochemical results were obtained regardless of the R group (Table 1c.6, entries 1, 3 and 5). For R = CO_2Me and CH_2OTBS, cycloadduct **1c.170** was favored in excellent overall yields, whereas the formyl substituted cyclopropane resulted in decomposition as with **1c.166**. However, in general the *cis*-substituted **1c.169** did not benefit for the most part by switching catalysts to $[Rh(CO)_2Cl]_{1c.}$ Enyne **1c.169** still

provided cycloadduct **1c.170** exclusively in excellent yield and regioselectivity, except when R = CO_2Me (entry 6). In this case a nearly equal mixture of **1c.170** and **1c.171** was produced. Interestingly, the formyl substituted cyclopropyl enyne **1c.169** gave an excellent yield of exclusively cycloadduct **1c.171** resulting from cleavage of the more substituted cyclopropane bond, a result congruent with that which was observed in the *trans* series (entry 4). The experimental results depicted in Tables 1c.5 and 1c.6 seem to indicate that cyclopropyl enynes in which the ring is substituted by a formyl group constitute a unique class of substrates in which the more substituted cyclopropane bond is preferentially cleaved in the [5+2] cycloaddition regardless of the rhodium catalyst.

Table 1c.6. The [5+2] cycloaddition of *cis*-2-substituted-1-vinylcyclopropanes.

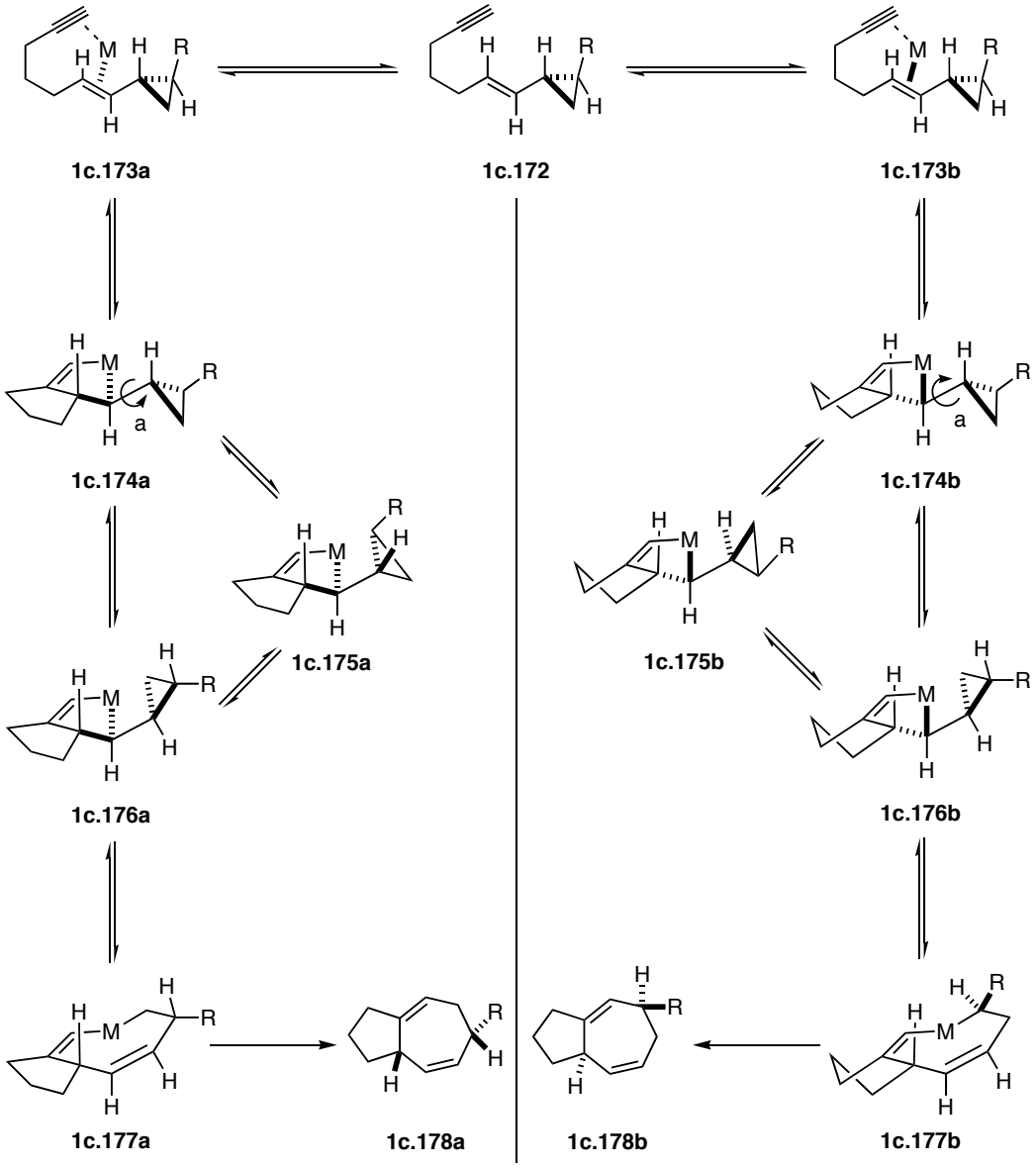


1c.169 **1c.170** **1c.171**

Entry	*R*	*Catalyst*	*Yield (%)*	*1c.170:1c.171*
1	CH_2OTBS	$Rh(PPh_3)_3OTf$	81	1:0
2	CH_2OTBS	$[Rh(CO)_2Cl]_2$	96	1:0
3	CHO	$Rh(PPh_3)_3OTf$	decomposition	-
4	CHO	$[Rh(CO)_2Cl]_2$	92	0:1
5	CO_2Me	$Rh(PPh_3)_3OTf$	85	6.4:1
6	CO_2Me	$[Rh(CO)_2Cl]_2$	98	1b.5:1

A mechanistic rational for the formation of regio- and diastereomers in the [5+2] cycloaddition has been proposed (Scheme 1c.10).[235,237] As is illustrated, the formation of the specific cycloadduct corresponds to the nature of the initial metal-π system coordination event to enyne **1c.172** at the onset to provide either **1c.173a** or **1c.173b**. Subsequent cyclometallation produces the initial metallocycles **1c.174a** and **1c.174b**. Bond rotation about carbon-carbon bond ***a*** aligns one of two cyclopropyl carbon-carbon bonds *syn* to the carbon-metal bond, thereby allowing for concerted ring expansion. A critical factor in determining whether metallocycles **1c.175** or **1c.176** will undergo migratory insertion relies on the geometrical *syn* requirement of the two protons necessary for formation of the resulting *cis* carbon-carbon double bond in the products. This factor requires that only one of the two possible cyclopropyl carbon-carbon bonds can be aligned properly with the carbon-metal bond to yield a [5.3.0] bicycle. Subsequent ring expansion of **1c.176a/b** followed by reductive elimination of the metal catalyst provides cycloadducts **1c.178a/b**. This mechanistic rationale suggests that the regioselectivity observed is a result of the initial π-facial selectivity in the formation of diastereomeric intermediates. Due to the remote nature of the R group in the formation of intermediates **1c.174-1c.176**, the regioselectivity is thus believed to be a direct result of the reversible nature of the preliminary mechanistic steps. This equilibrium then allows for either a favorable or unfavorable interaction between the R group and the rest of the molecule at a later stage. If this interaction results in a high-energy intermediate, the reaction can funnel back upstream in the proposed mechanistic sequence. Subsequent decomplexation/recomplexation of the metal to form either intermediate **1c.173a** or **1c.173b** and reaction down the opposite, presumably more energetically favorable pathway would provide the level of selectivity observed in these reactions.

Scheme 1c.10



The diastereoselectivity in the [5+2] cycloaddition arises from a combination of two events in the mechanistic outline depicted in Scheme 1c.10. First, the alkene facial selectivity of the initial coordination event to provide **1c.173a/b** dictates the bridgehead substituent's orientation. Then, alignment of one cyclopropane bond to allow for metal-

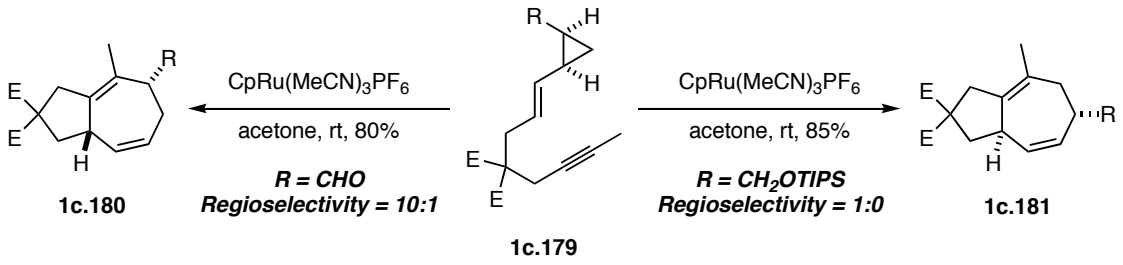
mediated ring expansion sets the relative stereochemistry. The studies Wender has performed on the regioselectivity of the reaction can by summarized in a few general trends. The $Rh(PPh_3)_3OTf$ catalyst system generally yields cycloadducts resulting from cleavage of the less-substituted cyclopropane bond regardless of cyclopropane stereochemistry and for most R-groups. On the other hand, $[Rh(CO)_2Cl]_2$ exhibited a reversal in regiochemistry in the *trans*-series of cyclopropyl enynes, and proved capable of catalyzing the reaction of formyl-substituted substrates. However, the *cis*-series yielded similar results to what $RhCl(PPh_3)_3$/AgOTf produced with the exception that the formyl-substituted cyclopropyl enyne gave the product resulting from cleavage of the more substituted cyclopropane bond. Therefore, it appears that $[Rh(CO)_2Cl]_2$ is a more versatile catalyst, and the desired diastereo- and regioselectivity can be obtained by constructing a substrate with the right combination of cyclopropane stereochemistry and functional group substituent on the ring.

1.C.3.3 Ruthenium-Catalyzed Intramolecular [5+2] Cycloadditions

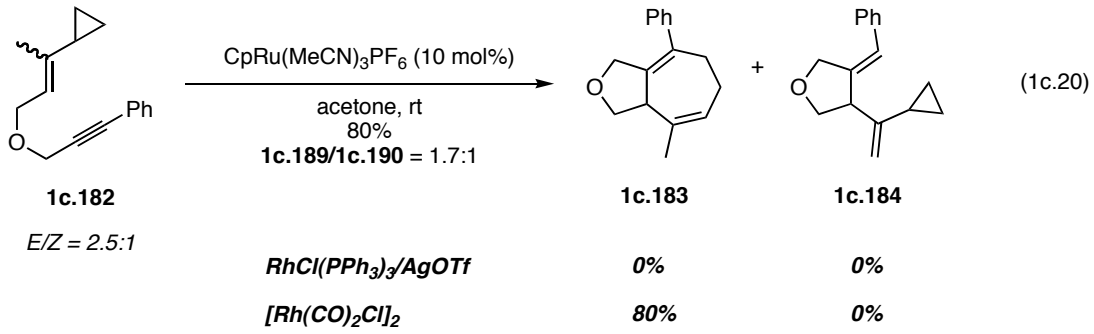
In 2000, Trost and coworkers described how a ruthenium complex was capable of mediating the same intramolecular [5+2] cycloaddition which Wender had developed utilizing rhodium(I) catalysis.[238] Although the overall transformation remained the same with only the nature of the catalyst changing, a different set of results was obtained regarding the regio- and diastereoselectivity in the product distribution for some substrates. A sample of the most intriguing results is illustrated in Scheme 1c.11. When the formyl-substituted *cis* cyclopropylenyne **1c.179** was treated with the cationic ruthenium species, cycloadduct **1c.180** was obtained with complete regiocontrol as a mixture (10:1) of diastereomers. However, if the silyl protected methyl carbinol-substituted substrate **1c.179** was used, *syn*-cycloadduct **1c.181** was obtained. The

formation of **1c.181** follows the same regio- and diastereomeric trends that Wender observed in the rhodium-catalyzed [5+2] cycloaddition. Even though the regiochemistry observed in the formyl substituted case is also in line with Wender's results, the diastereoselectivity is quite different. In general however, the diastereoselectivity of the reaction is quite high, and the authors report that the incomplete reversal of diastereocontrol in the cycloaddition of formyl-substituted **1c.179** is a result of the enolizability of the aldehyde functionality.

Scheme 1c.11

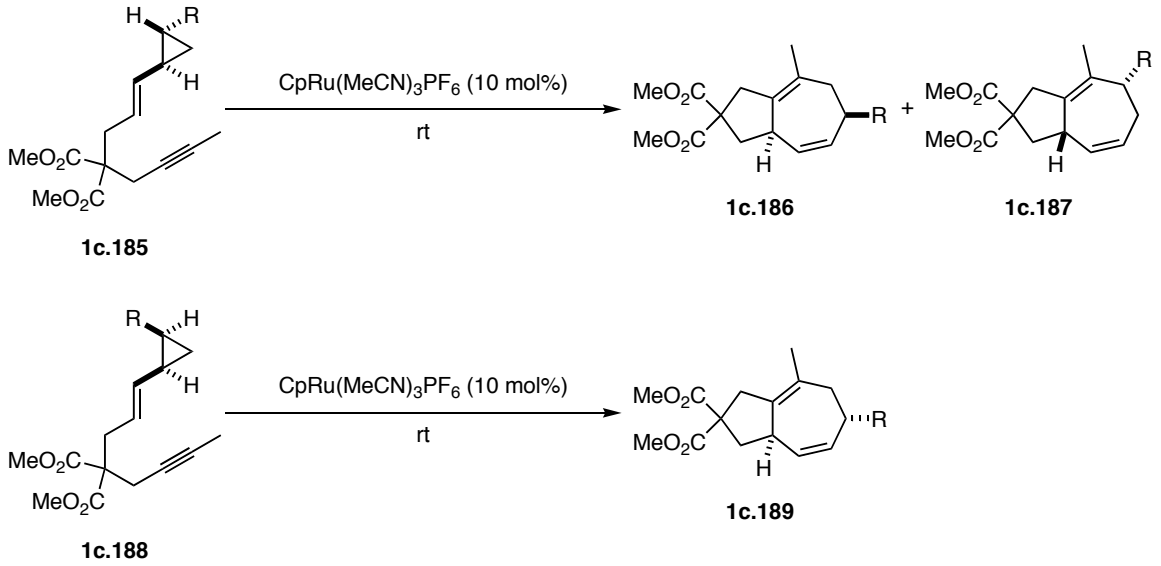


When ether **1c.182** was treated with the cationic ruthenium species, a mixture (1.7:1) of cycloadducts **1c.183** and **1c.184** was obtained (Eq. 1c.20). However, when the same substrate was treated with the cationic Wilkinson's catalyst system reported by Wender, a complex mixture containing none of the desired cycloadduct or cycloisomerized product was obtained. When $[Rh(CO)_2Cl]_2$ was used to catalyze the cycloaddition, an 80% yield of only cycloadduct **1c.183** was obtained. These strikingly different results seem to indicate that there exists at least subtle differences in the mechanistic pathway of the rhodium-catalyzed [5+2] cycloaddition and the cationic ruthenium variant.



In general, Trost reported that the cationic ruthenium-catalyzed [5+2] cycloaddition provided regio- and diastereomeric results similar to those Wender observed in the rhodium-catalyzed reaction.[239] The *trans*-substituted cyclopropyl enynes produced cycloadducts containing an *anti* relative stereochemical configuration across the ring, whereas the corresponding *cis*-substrates produced the *syn*-cycloadducts. In most cases, the cationic ruthenium catalyst produced mixtures (3:1 to 1:2.5) of cycloadducts **1c.186** and **1c.187** for the *trans*-substituted cyclopropane substrates (Scheme 1c.12). Once again though, the case in which R = CHO proved anomalous, providing cycloadduct **1c.187** as a mixture (15:1) of regioisomers in excellent yield. Additionally, treatment of **1c.188** (R = CHO) with the cationic ruthenium species produced cycloadduct **1c.189** with complete regio- and diastereoselectivity. The aldehyde substrates present a unique situation in which the exact balance of steric and electronic effects provide results that differ markedly from others. The *cis*-substituted cyclopropyl enynes also gave similar results with ruthenium as was found with rhodium by providing primarily cycloadduct **1c.189** in excellent yield and regioselectivity. The advantages of ruthenium catalysis over the rhodium variant of this reaction seem to be limited simply to the milder conditions required for ruthenium. Namely, the reactions are run under a 100 ˚C in toluene for rhodium vs. room temperature in acetone for ruthenium.

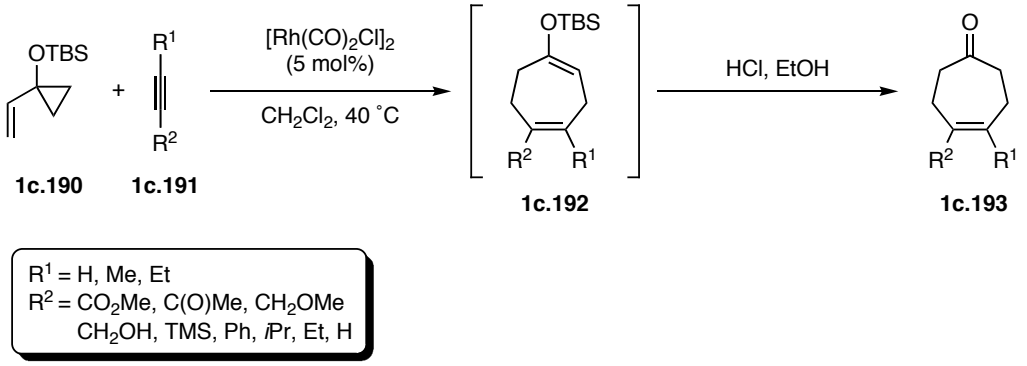
Scheme 1c.12



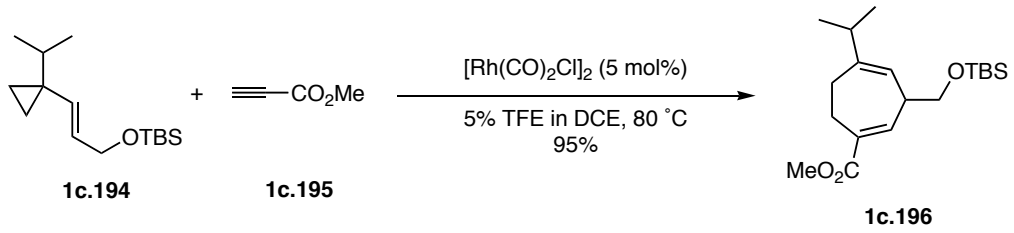
1.C.3.4 The Transition Metal-Catalyzed Intermolecular [5+2] Cycloaddition

To follow the studies Wender and coworkers reported in 1995 on the intramolecular [5+2] cycloadditions, the first intermolecular [5+2] cycloaddition of vinyl cyclopropanes and alkynes was described in 1998 as a homologous Diels-Alder reaction.[240] In these initial studies, the authors report the need for an activated siloxycyclopropane **1c.190** to facilitate the reaction with various alkynes **1c.191**, thereby providing the corresponding seven-membered ring ketones **1c.193** upon subsequent hydrolysis of the resulting silyl enol ether **1c.192** (Scheme 1c.13). Vinyl cyclopropanes lacking an oxygen substituent were unreactive under the reaction conditions. However, the scope of the alkyne was quite general in that the reaction proceeded whether electron poor or rich, internal or terminal alkynes were employed.

Scheme 1c.13



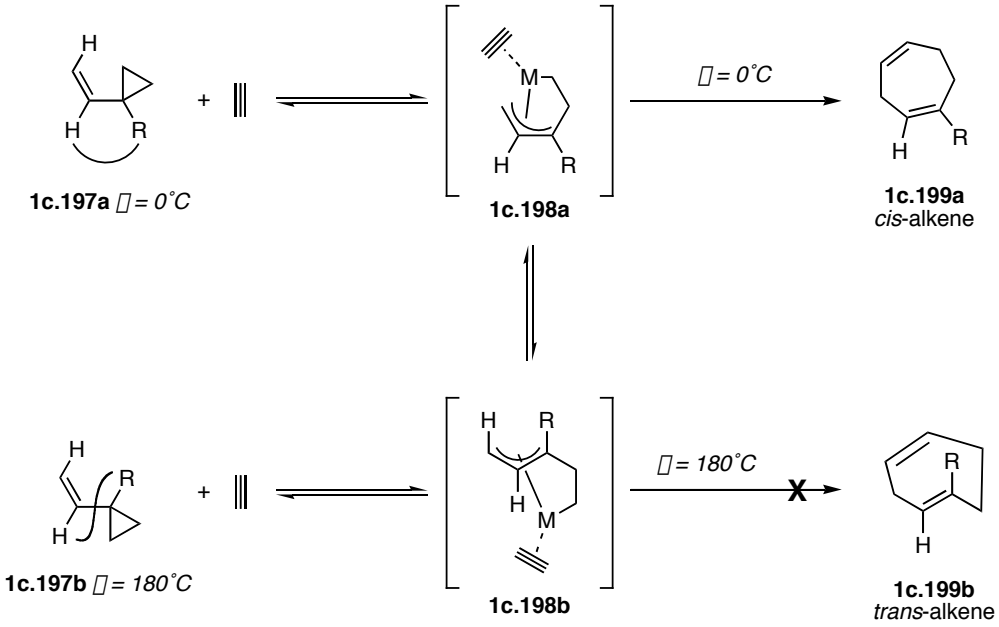
However, Wender and coworkers reported in 2001 that unactivated vinylcyclopropanes were in fact useful substrates in the intermolecular [5+2] cycloaddition reaction.[241] Vinyl cyclopropanes **1c.194** containing an additional alkyl substituents at the 1-position were shown to react smoothly with alkyne **1c.195** in the presence of $[Rh(CO)_2Cl]_2$ to provide the corresponding cycloadducts **1c.196** in excellent yield and with complete regioselectivity (Eq. 1c.21). The excellent regioselectivity observed is believed to be a result of the unfavorable steric interaction between the vinyl substituent and methyl ester. If a terminal alkene is present in the vinyl cyclopropane, the reaction produces an equal amount of both regioisomers. A number of different alkyne substituents proved viable substrates in the cycloadditions of siloxy substituted vinyl cyclopropanes.



(1c.21)

These studies suggest that the presence of an oxygen substituent at the 1-position of vinylcyclopropanes is not critical. Rather a quaternary allylic carbon on the cyclopropane is all that is required to force the vinylcyclopropane into a favorable geometrical configuration. The presence of any R group has been shown to reduce the energy differences between the *s*-cis **1c.197a** and *s*-trans **1c.197b** conformers (Scheme 1c.14). Naturally, as R increases in size the energy effect is likewise increased thereby diminishing the difference. This effect on the conformers could increase the likelihood of forming *Z*-allyl intermediate **1c.198a** over the *E*-allyl **1c.198b**. The requirement of a *cis*-alkene in the product then requires that **1c.198a** undergoes cyclization to provide **1c.199a** whereas **1c.198b** can only proceed to the improbable *trans* cycloadduct **1c.199b**.[242]

Scheme 1c.14



1.C.3.5 Summary

In summary, a vast amount of work has been accomplished on the transition metal-mediated [5+2] cycloaddition reaction. The reaction has been shown to be widely applicable to a variety of substrates tolerating various substitution patterns on the cyclopropane and both π-systems involved in the carbocyclization event. Additionally, high regio- and diastereoselectivity has been observed in the formation of cycloadducts from their corresponding cyclopropyl enynes. A unique level of regiocontrol has been illustrated by either designing the substrate with a particular functional group as the substituent on the cyclopropane, or choosing the proper rhodium(I) catalyst. The diastereoselectivity has been shown to arise from the relative configuration about the cyclopropane ring. One drawback to this transformation is that the stereochemical consequence of the reaction is relative, namely the optical purity of the cycloadduct is a direct consequence of how enantioenriched the starting enyne is. This issue may be addressed in one of two ways, by the future development of an enantioselective variant through the use of chiral ligands or synthesizing the cyclopropylenyne in enantiopure form. The latter is most efficiently accomplished through the coupling of the [5+2] cycloaddition with an asymmetric cyclopropanation to establish the absolute stereochemistry of the starting enyne. It should come as no surprise that this transition metal-catalyzed carbocyclization reaction has found applicability, and will continue to be valuable in the synthesis of complex natural products.[243,244]

1.C.4 The Transition Metal-Catalyzed Pauson-Khand Annulation

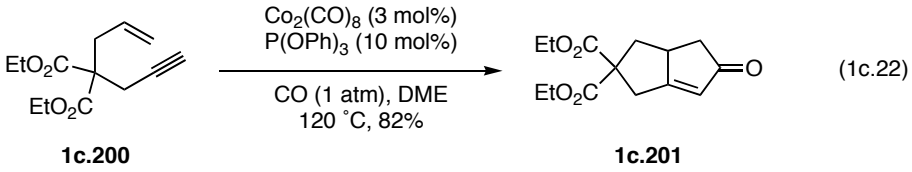
The Pauson-Khand reaction has quickly become of the most useful transition metal-catalyzed carbocyclization reactions available to the synthetic chemist in recent years.[127,128,139] Formally a [2+2+1] cycloaddition, the Pauson-Khand annulation involves

the three-component coupling of an alkene, alkyne and formally carbon monoxide to yield a cyclopentenone. The reaction was first discovered in the early 1970's and has since undergone incredible expansion with regards to efficiency and applicability.[245,246] Early work showed that this transformation suffered in scope and utility by requiring elevated temperatures and extended reaction times, the combination of which frequently led to decomposition of starting materials. Additionally, the Pauson-Khand reaction was limited to symmetrical, strained alkenes to mask the poor efficiency of the overall reaction, and eliminate the unavoidable mixtures of cyclopentenone regioisomers. The reaction was also found to be quite sensitive to the steric and electronic environment on both the alkene and alkyne. It was originally shown that stoichiometric dicobaltoctacarbonyl was able to effect this transformation, and this catalyst continues to be the primary transition metal complex for the Pauson-Khand reaction.

Since the seminal publication and subsequent work immediately following, a number of advances have been made toward making the PKR more efficient and broader in scope. In 1981, Schore discovered that the issue of alkene regiochemistry could be overcome by tethering the alkene and alkyne rendering the process intramolecular.[247] It has since been shown that the reaction can be performed catalytically and enantioselectively through the use of chiral ligands. Another important advance has been the discovery of a number of different transition metals capable of catalyzing the [2+2+1] cycloaddition, thereby further broadening the scope of this reaction.

One of the most significant advances made in the PKR was reported by Rautenstrauch and coworkers when they showed that the cycloaddition of a *non-strained* alkene could be effected with 1a.22 mol% of $Co_2(CO)_8$ under a relatively high CO pressure (100 bar) in 47% yield.[248] The authors proposed that the cobalt catalyst had the tendency to aggregate into an inactive species under the previously reported reaction

conditions, and thus lead to a decrease in yield. Jeong was the first to show that through the use of phosphite ligands, the active cobalt species could be stabilized, thus providing the corresponding cyclopentenone in good yield. Thus, when enyne **1c.200** was treated with 3 mol % $Co_2(CO)_8$ in the presence of 10 mol% $P(OPh)_3$ under one atmosphere of carbon monoxide, the corresponding PKR product **1c.201** was obtained in 82% yield (Eq. 1c.22). [249]



1c.200 **1c.201** (1c.22)

A number of important contributions to the cobalt-catalyzed PKR have since been made, further increasing the efficiency and scope of the reaction. First, Livinghouse noted that the use of high purity $Co_2(CO)_8$ was critical in achieving a good conversion for both the thermal and photochemical PKR.[250] Additionally, Sugihara reported that hard Lewis bases, which are known to labialize the ligands on low-valent metal complexes, can be employed to promote otherwise difficult cycloadditions.[251] Notably, the use of 1,2-dimethoxyethane (DME) as solvent was the most efficient promoter of the PKR catalyzed by $Co_2(CO)_8$.

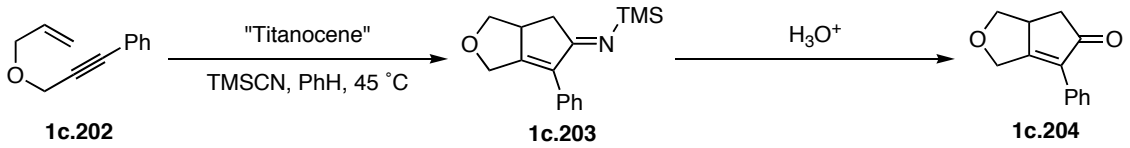
In recent years, the focus has shifted toward the use of other transition metal catalysts to promote the Pauson-Khand reaction. The discovery of other PKR catalysts have enabled a number of previously problematic substrates to undergo the desired carbocyclization to yield the corresponding cyclopentenones, thereby leading to a resurgence of this [2+2+1] cycloaddition in the synthesis of natural products. Zirconium,[252] nickel[253] and molybdenum[254] carbonylated species were found to be viable

catalysts providing the corresponding bicyclic enones in good yields. Iron,[255] titanium[256] and tungsten[257] complexes have also found their way into the realm of PKR catalysts. More recently, ruthenium[258,259] and rhodium[260,261] carbonyl catalysts have shown wide applicability in providing the desired [2+2+1] cycloadducts.

1.C.4.1 Titanium-Catalyzed Pauson-Khand Annulations

Buchwald and coworkers showed in the early 1990's that a number of titanocene complexes were capable of catalyzing the Pauson-Khand reaction in good to excellent yields.[262,263] The use of chiral ligands on the titanium metal center has since led to an enantioselective variant of the cycloaddition, providing enantioenriched cyclopentenones in good yield and enantioselectivity.[264] In 1993, Buchwald showed that the use of a (trialkylsilyl)cyanide could serve as a CO surrogate in the presence of a titanocene complex to catalyze the PKR of enyne **1c.202**. The cycloaddition yields an intermediate imine **1c.203**, which upon acid hydrolysis affords the desired bicyclic enone **1c.204** (Table 1c.7).

Table 1c.7. PKR catalyzed under CO-free conditions



1c.202 **1c.203** **1c.204**

Entry	*Catalyst*	*Mol%*	*Yield (%)*
1	$Cp_2Ti(PMe_3)_2$	10	80
2	Cp_2TiCl_2/*n*-BuLi	10	82
3	$Ni(COD)_2$/Ligand	5	60

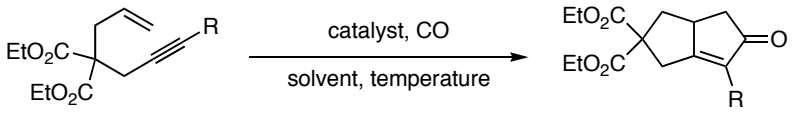
1.C.4.2 Ruthenium- and Rhodium-Catalyzed Pauson-Khand Reactions

Although the catalysts mentioned *a priori* have demonstrated their utility in catalyzing the PKR with good to excellent results, much of the work reported recently has been utilizing ruthenium and rhodium species to facilitate the cycloaddition. Ruthenium was the first of these metals to show applicability in catalyzing the PKR of enyne substrates. Murai[259] and Mitsudo[258] reported independently the ruthenium-catalyzed PKR of enyne **1c.205** in the presence of 2 mol% $Ru_2(CO)_{12}$ to yield bicyclic enone **1c.206** in 86% yield (Table 1c.8, entry 1). To achieve satisfactory yields with this ruthenium species, elevated CO pressures were necessary, and the choice of solvent was critical.

The use of rhodium complexes to catalyze the PKR has been the focus of a number of endeavors among different research groups recently.[260,261,265-267] The use of various rhodium(I) catalysts have been shown to catalyze the PKR of previously troublesome substrates, as well as some novel [2+2+1] cycloadditions. Narasaka was one

of the first to illustrate that as little as 1 mol% of $[Rh(CO)_2Cl]_2$ was capable of catalyzing the intramolecular Pauson-Khand reaction of enynes **1c.205** to yield the corresponding enones **1c.206** in good to excellent yields (Table 1c.8, entry 2). In the same year, Jeong reported the use of $[Rh(CO)(dppp)Cl]_2$ as an effective PKR catalyst under 1 atm of CO to yield the desired product in excellent yield (entry 3).

Table 1c.8. Ruthenium- and rhodium-catalyzed Pauson-Khand reaction



1c.205 **1c.206**

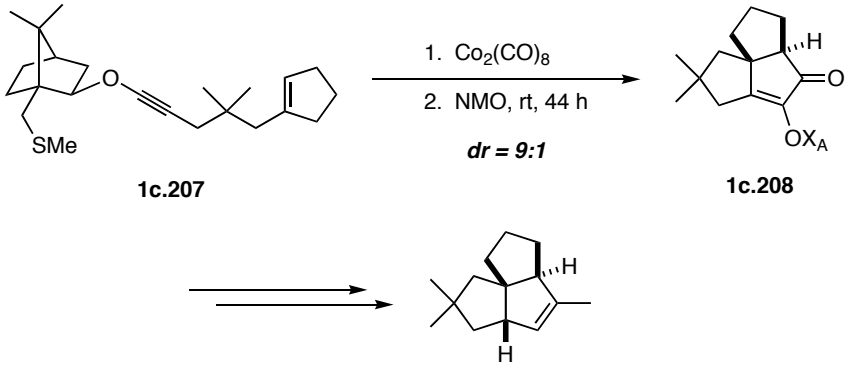
Entry	*R*	*Catalyst*	*Mol%*	*CO Pressure (atm)*	*Yield (%)*	*Solvent*
1	Me	$Ru_2(CO)_{12}$	2	10-15	86	dioxane
2	Ph	$[Rh(CO)_2Cl]_2$	1	1	94	Bu_2O
3	Ph	$[Rh(CO)(dppp)Cl]_2$	1c.5	1	99	PhMe

1.C.4.3 The Enantioselective Pauson-Khand Reaction

In the past decade focus has been geared toward rendering the Pauson-Khand reaction enantioselective. The methods which have proven to be the most successful either incorporate a chiral auxiliary in the substrate to render the process diastereoselective by starting with enantioenriched substrates or enable asymmetry through the use of chiral ligands on the metal complex. Chiral promoters have also seen applicability although their use has been rather limited and have not seen the attention which other methods have been afforded.

Pericas and Riera have pioneered the use of chiral auxiliaries in the asymmetric PKR.[268] The method developed incorporates a sulfur moiety appropriately positioned to coordinate to the cobalt-alkyne complex thereby rendering the process diastereoselective. For example, when the chiral camphor-derived enyne **1c.207** was treated with dicobaltoctacarbonyl, the tricyclic intermediate **1c.208** was produced as a mixture (9:1) of diastereomers (Scheme 1c.15). This intermediate was then advanced to the tricyclic natural product (+)-15-nor-pentalenene (**1c.209**).[269]

Scheme 1c.15



1c.207 **1c.208**

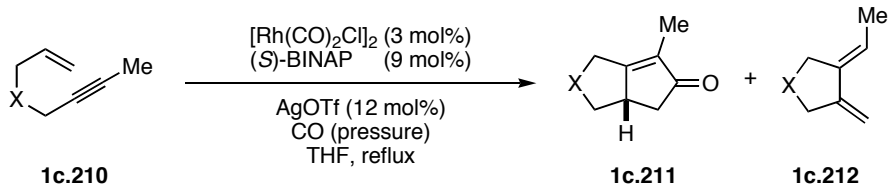
(+)-15-nor-pentalenene **(1c.209)**

Attempts to render the transition metal-catalyzed Pauson-Khand reaction enantioselective through the use of chiral catalysts have not, until recently, produced fruitful results. Early work suggested that stoichiometric chiral catalyst in conjunction with high CO pressures and elevated temperatures were necessary to impart asymmetric induction, but more recently a chiral catalyst has been reported that eliminate the need to use such rigorous conditions. One of the main difficulties in this reaction is that most late transition metals require that CO ligands be present for the catalyst to exhibit useful levels of catalytic activity. Unfortunately, carbon monoxide is a non-tunable, extremely strong π-acceptor ligand for the late transition metals that have a high electron density

around their center. Therefore, the introduction of chiral ligands displace CO, thereby rendering the catalyst less efficient, and subsequently leading to a rather difficult catalytic processes.[270] Buchwald showed in 1996 that the chiral titanium catalyst, (*S,S*)-(EBTHI)Ti$(CO)_2$, was capable of inducing asymmetry.[264] The use of cobalt species in the presence of BINAP ligands has also shown promise, but with limited success.[271]

In 2000, Jeong reported the use of $[Rh(CO)_2Cl]_2$ in the presence of BINAP ligands as an effective enantioselective catalyst system for the PKR.[270] When enynes of type **1c.210** were treated with bisphosphine ligand and the rhodium(I) catalyst in the presence of AgOTf under an atmosphere of CO, the desired bicyclic enones **1c.211** could be obtained in good yield and excellent enantioselectivities (≥ 96% *ee*) (Table 1c.9). The use of a silver salt was found to be crucial in the initiation of the reaction. Additionally, finding the optimal pressure of CO was necessary to obtain the right balance of high yield and enantioselectivity. Although a low pressure of CO was most favorable for enantiocontrol, significant amounts of the 1,4-diene byproduct **1c.212**, resulting from cycloisomerization of the enyne, effectively lowered the chemical yield of the process.

Table 1c.9. Asymmetric Rh(I)-catalyzed Pauson-Khand reaction

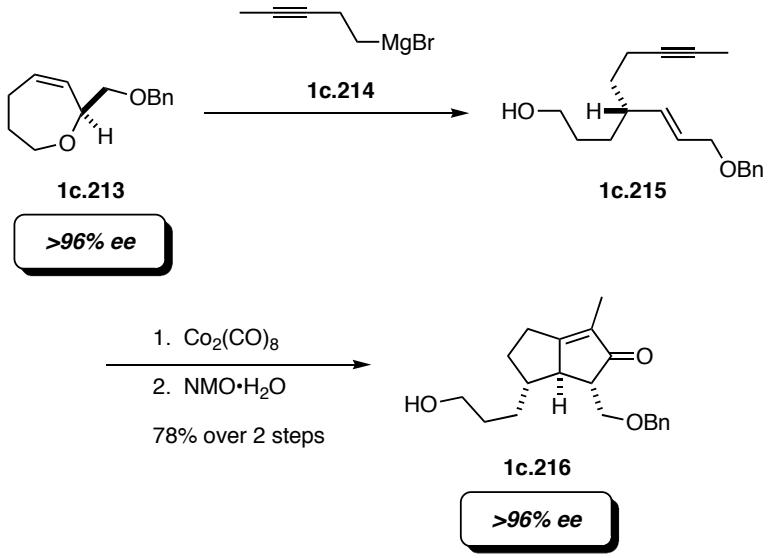


1c.210 **1c.211** **1c.212**

Entry	*X*	*CO Pressure (atm)*	*Yield of 1c.211 (%)*	*ee (%)*
1	$C(CO_2i\text{-}Pr)_2$	1	40	90
2	O	2	85	86
3	O	1	40	96

Alternatively, diastereoselective Pauson-Khand cycloadditions of enantioenriched starting materials have also found applicability, particularly in the total synthesis of natural products. In 1997, Hoveyda showed how a stereoselective alkylation of enantioenriched allyl ether **1c.213** (>96% *ee*) with homopropargyl Grignard reagent **1c.214** could be used to assemble the 1,6-enyne **1c.215** (Scheme 1c.16).[272] Treatment of **1c.215** with dicobaltoctacarbonyl provided the corresponding PKR product **1c.216** in excellent yield and with complete diastereoselectivity.

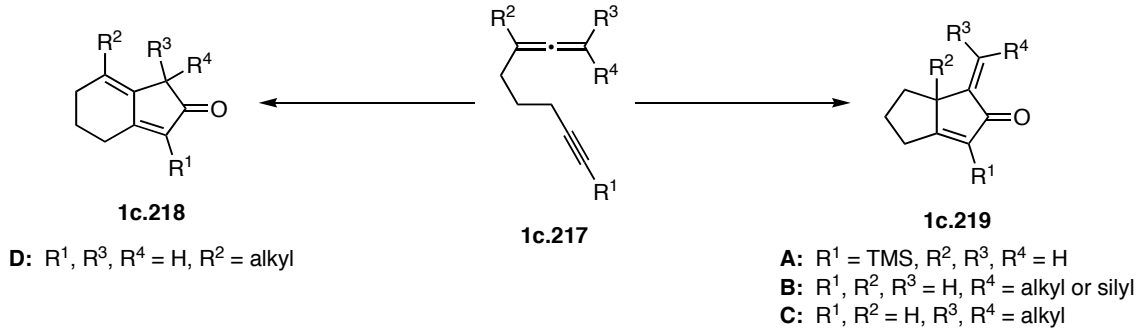
Scheme 1c.16



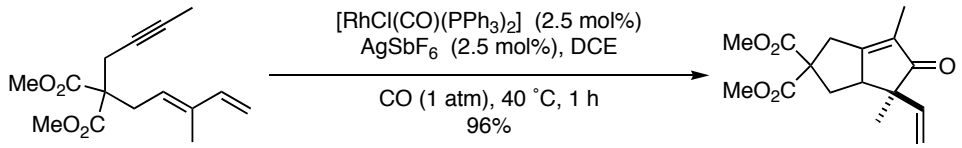
1.C.4.4 Alternative [2+2+1] Cycloaddition Substrates: The Allenic and Dienyl Pauson-Khand Type Reactions

Recently attention in the synthetic community has shifted toward developing not only better methods of realizing the [2+2+1] cycloaddition, but also discovering new starting materials that could be employed for the assembly of more structurally complex intermediates. One class of substrates that has received a great deal of study has been the cycloaddition of allenynes to establish a useful allenic Pauson-Khand-type of transformation.[265,266,273] Starting from allenyne **1c.217**, the absence of an R^2 alkyl substituent routinely yields cycloadducts **1c.219** (Scheme 1c.17). However, if the allene is 1,1-disubstituted, bicyclic enones **1c.218** are obtained. Whether one cycloadduct or the other is formed preferentially is dependent upon which allenic olefin participates in the carbocyclization event, which in turn is dependent upon the substitution pattern within the substrate.

Scheme 1c.17

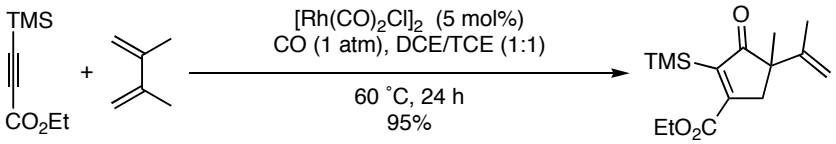


A number of research groups have recently focused on developing the dienyl Pauson-Khand annulation. Wender and coworkers demonstrated in 2003 the first intramolecular dienyl PKR sequence catalyzed by the rhodium(I) species, $[RhCl(CO)(PPh_3)_2]$.[274,275] When dieneyne **1c.220** was treated with the rhodium(I) catalyst in the presence of $AgSbF_6$ under 1 atm of CO, the corresponding bicyclic enone **1c.221** was obtained in excellent yield (Eq. 1c.23). The following year, Wender reported the first intermolecular variant of the dienyl Pauson-Khand reaction thereby expanding the scope of this reaction.[276] He showed that when disubstituted alkynes **1c.222** in the presence of 1,4-dienes **1c.223** were treated with the rhodium(I) species, $[Rh(CO)_2Cl]_2$, cyclopentenone **1c.224** was obtained regioselectively in 95% yield.



(1c.23)

1c.220 **1c.221**



(1c.24)

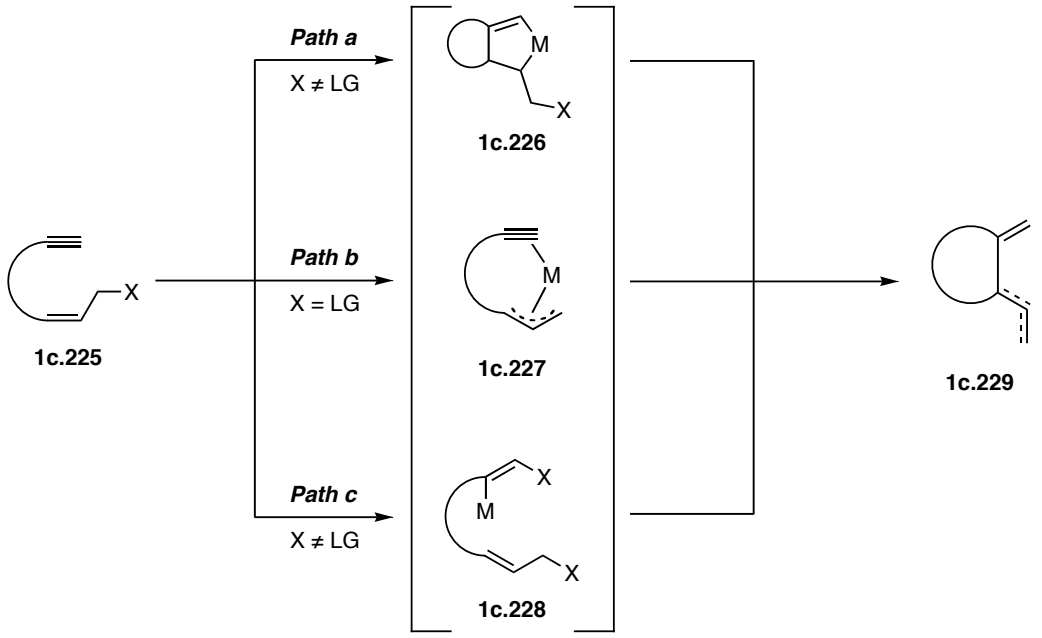
1c.222 **1c.223** **1c.224**

1.C.5 Transition Metal-Catalyzed Cycloisomerizations

With synthetic organic chemistry evolving as it has toward the rapid construction of complex intermediates through one step sequences starting from relatively simple starting materials, the use of transition metal-catalyzed methods have taken a lead role in this endeavor. The transition metal-catalyzed cycloisomerization of 1,*n*-enynes, 1,*n*-dienes and 1,*n*-diynes has been established as a critical method in which such transformations are possible.[140] Although the development of cycloisomerization methodology to include diene and diyne substrates has greatly expanded the scope of this reaction, in this discussion we will primarily focus on the use of enynes as substrates. There exists three different mechanistic pathways whereby a transition metal catalyst can interact with a 1,*n*-enyne as illustrated in Scheme 1c.18. Most transition metals react with enyne **1c.225** by first complexation to both π-systems, followed by oxidative addition to yield the metallocyclopentene **1c.226** depicted by *Path a*. Alternatively, if the substrate were to incorporate a leaving group in the allylic position, the π-allyl complex **1c.227** could be formed that can then undergo reaction with the pendant alkyne (*Path b*).

Finally, hydrometallation of the alkyne to yield the vinyl metal species **1c.228** encompasses the final possibility for a transition metal catalyst (*Path C*). Subsequent reaction of **1c.226-1c.228** forms the carbocyclic product **1c.229**. The discussion here will be limited to those reactions which are thought to undergo metallocyclopentene **1c.226** formation *via* path a.

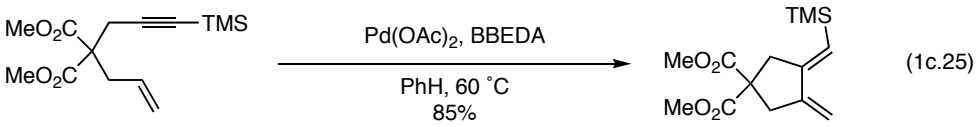
Scheme 1c.18



1.C.5.1 Palladium-Catalyzed Cycloisomerizations

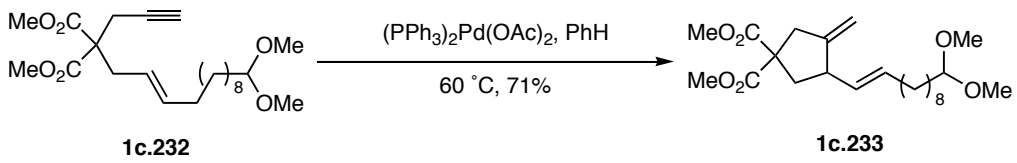
A number of different metals have been shown to catalyze the cycloisomerization of enynes to the corresponding carbocyclic products.[133,140] However, the vast majority of work in this field has focused primarily on palladium-catalyzed processes.[134] Preliminary findings showed that when a substrate such as enyne **1c.230** was treated with $Pd(OAc)_2$ in the presence of the bisimine ligand BBEDA, the 1,3-diene **1c.231** was obtained exclusively.[277] The reaction is selective for the conjugated dienes when the starting enyne

lacks allylic hydrogens. Additionally, the effects of substituents on the tether between the alkene and alkyne did not produce a dramatic effect on the efficiency of the reaction. The presence of the *gem* diester moiety and a protected propargylic alcohol both seemed to increase the rate of the reaction relative to the presence of simple alkyl or the complete lack of substitutents.[278]

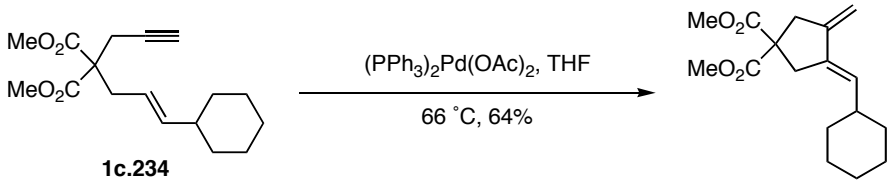


1c.230 **1c.231** (1c.25)

In palladium catalyzed cycloisomerizations, the nature of the diene formed in the cyclized products is partially dependent on the steric influences present in the starting material.[277,279] For enynes containing an allylic methylene as represented by **1c.232**, 1,4-diene **1c.233**, a net Alder-ene type product, was obtained regioselectively in 71% yield (Eq. 1c.26). However, if there is branching at the allylic position as in **1c.234**, product distribution was completely reversed, providing the conjugated 1,3-diene **1c.235** in good yield (Eq. 1c.27). Additionally, the presence of a protected allylic alcohol produced the 1,3-diene products, where if the protected hydroxyl was in the homoallylic position, the 1,4-diene was produced. It has been proposed that the regiocontrol observed by an allylic or homoallylic oxygen substituent was a product of electronic influences.[280] In addition to these electronic factors, whether the allylic methylene contains branching or not directs the regiochemistry of β-elimination due to the presence of unfavorable steric interactions. These results seem indicate that in palladium-catalyzed cycloisomerizations a discrete balance of steric and electronic factors influence the regiochemistry.



1c.232 1c.233 (1c.26)

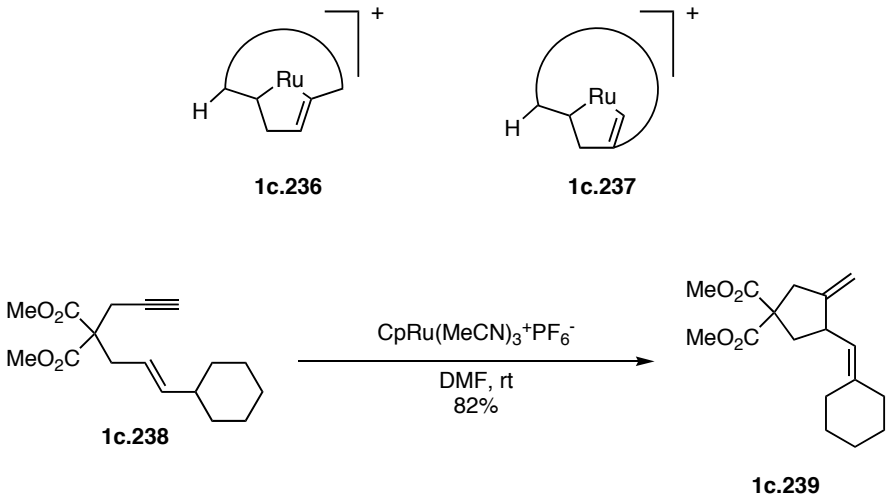


1c.234 1c.235 (1c.27)

1.C.5.2 Ruthenium-Catalyzed Cycloisomerizations

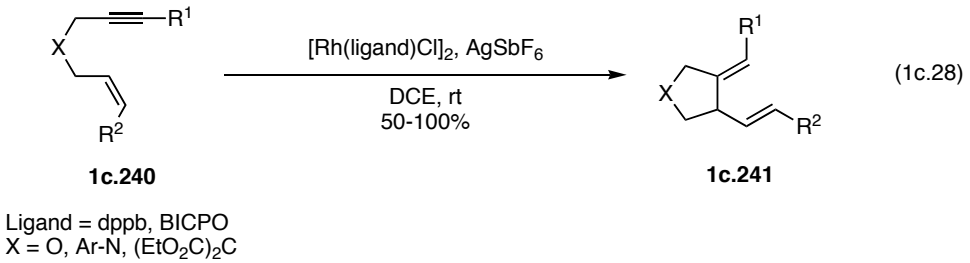
The scope of the transition metal-catalyzed cycloisomerization reaction has been expanded to include the use of ruthenium complexes. Initial work utilizing the CpRu(cod)Cl species to catalyze the cycloisomerization reaction proved efficient on unactivated enynes, unfortunately only monosubstituted alkenes were viable substrates.[281] The authors proposed that the alkene substituent must be attached to the ruthenium complex to allow for β-elimination as illustrated in structure **1c.235** and **1c.236** (Scheme 1c.19). This would then lead to 1,3-bridging that cannot occur if a shorter tether is employed. However, recently Trost illustrated the use of the ruthenium complex, $CpRu(MeCN)_3^+PF_6^-$, in the cycloisomerization of 1,2-disubstituted alkene **1c.237** to provide the 1,4-diene **1c.238** regioselectively in 82% yield.[282] With this ruthenium species, *trisubstituted* olefins are well tolerated in the carbocyclization, producing results similar to those obtained under palladium catalysis. Although the mechanism is thought to proceed through a ruthenacyclopentene, the possibility exists that a π-allyl intermediate may actually be involved.[283]

Scheme 1c.19



1.C.5.3 Rhodium- and Iridium-Catalyzed Cycloisomerizations

Much of the synthetic efforts in the context of transition metal-catalyzed cycloisomerizations in recent years has focused on the development of rhodium-catalyzed processes.[284] In most cases, it was found that rhodium(I) complexes in the presence of silver salts provided superior results in catalyzing the desired transformation as compared to those reactions run in the absence of any additives. The best results were obtained when the cycloisomerization of *cis*-enyne **1c.240** was catalyzed by a rhodium(I) species in the presence of either dppb or BICPO ligands and $AgSbF_6$ to yield 1,4-diene **1c.241** in moderate to excellent yields (Eq. 1c.28). By tuning the bisphosphine ligand the reaction conditions could be easily optimized for each substrate. Recently, the first asymmetric cycloisomerization of 1,6-enynes was reported by employing the chiral Me-DuPhos ligands to achieve enantioselectivities as high as 95% *ee*.[285]

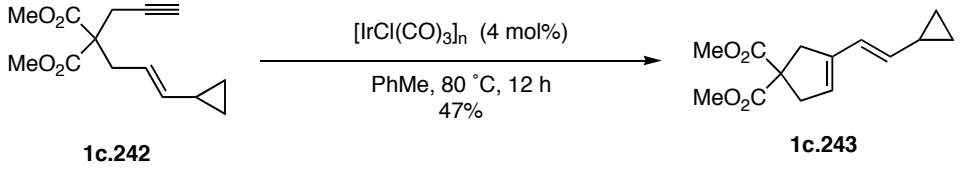


(1c.28)

1c.240 **1c.241**

Ligand = dppb, BICPO
X = O, Ar-N, $(EtO_2C)_2C$

Finally, Murai reported that the iridium complex $[IrCl(CO)_3]_n$ effectively catalyzed the cycloisomerization of 1,6-enynes.[286] For example, when enyne **1c.242** was treated with 4 mol% of $[IrCl(CO)_3]_n$, 1,3-diene **1c.243** was obtained in a moderate 47% yield as the sole product (Eq. 1c.30). The reaction of **1c.242** is unusual in that even though the enyne contains a vinyl cyclopropane moiety, no [5+2] cycloaddition product was obtained from the reaction. For a variety of other substrates, yields were reported to be as high as 99%.



(1c.29)

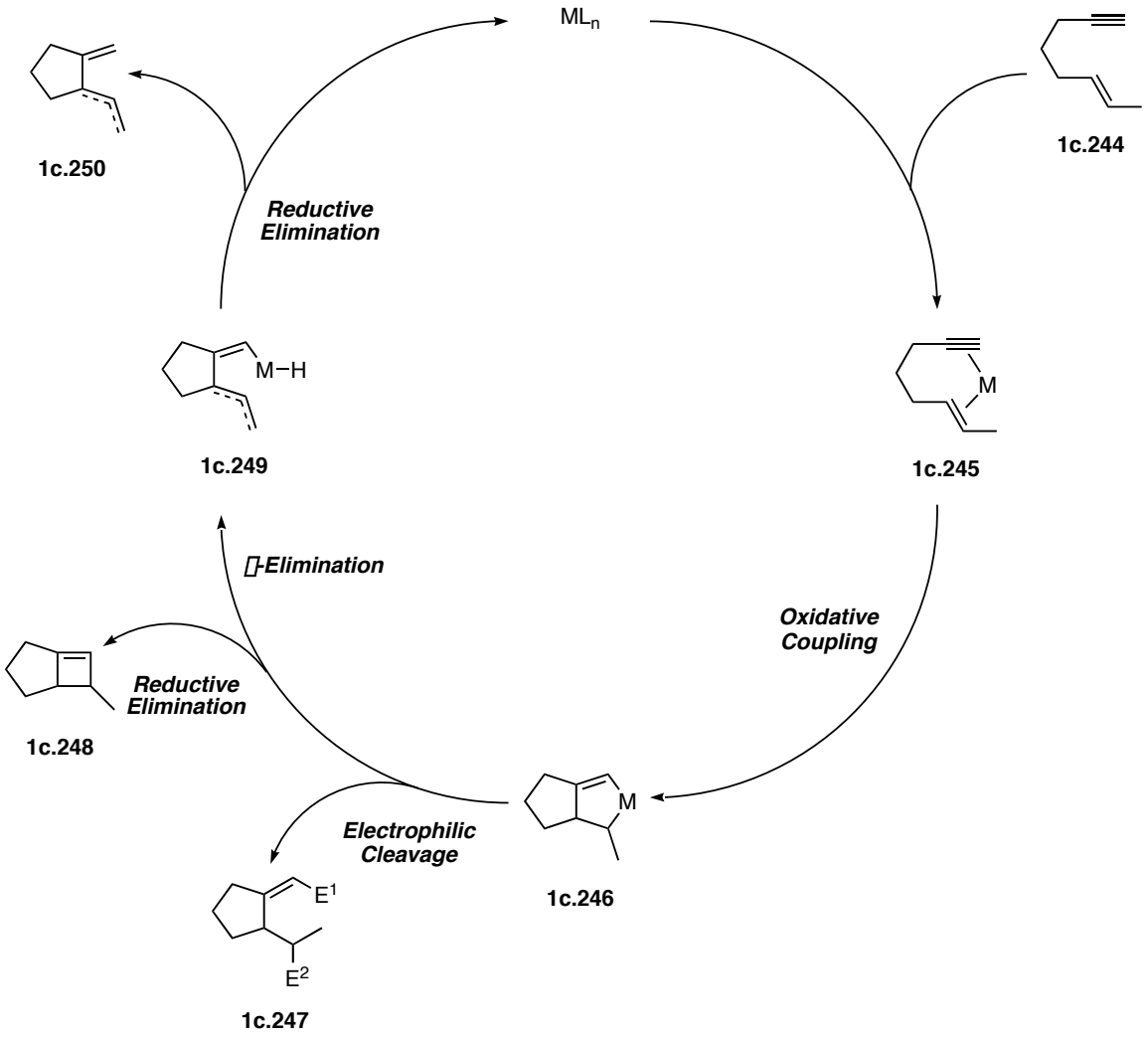
1c.242 **1c.243**

1.C.5.4 Mechanistic Discussion of the Transition Metal-Catalyzed Cycloisomerization of 1,6-Enynes

The formation of metallocyclopentenes from enyne substrates is a mechanistic pathway common in a wide array of transition metal-catalyzed reactions. The cycloisomerization begins when the metal species initially complexes simultaneously to the alkene and alkyne in enyne **1c.244** to form intermediate **1c.245** (Scheme 1c.20). Oxidative addition of the metal to the substrate occurs to yield metallocycle **1c.246**. At

this stage one of three different reaction events can take place depending upon the nature of the metal catalyst and substrate structure. If an electrophile is present, electrophilic cleavage of the metallocyclopentene can occur to yield the functionalized product **1c.247**. If the metal species, or the substitution in the substrate cannot undergo β-elimination, reductive elimination of the catalyst yields bicycle **1c.248**. The most likely pathway in these transformations involves β-hydride elimination to yield the vinyl metal species **1c.249**, which then undergoes reductive elimination to yield the cycloisomerization product **1c.250** and regenerate the active catalyst species.

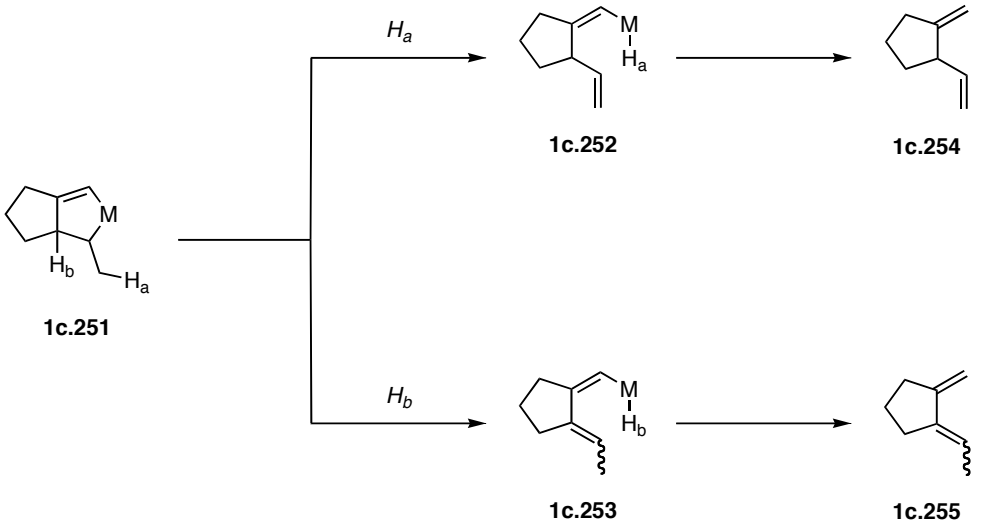
Scheme 1c.20



The regioselectivity in the β-hydride elimination step has been the subject of much scrutiny in this mechanistic hypothesis.[280,287] Depending upon which hydrogen the catalyst chooses to extract, either a 1,3- or 1,4-diene product is obtained. Two critical criteria must be met to allow for β-hydride elimination to occur. The first of these is that there must be an open coordination site on the metal to accommodate the resulting hydride species. The second criteria is that there must be a *cis* alignment of the carbon-

hydrogen and carbon-metal bonds to allow for maximum orbital overlap. As illustrated in Scheme 1c.21, a metallocyclopentene **1c.251** has two hydrogens, H_a and H_b from which abstraction could occur to yield one of two possible regioisomers **1c.252** and **1c.253**. Upon subsequent reductive elimination cycloisomerization products **1c.254** and **1c.255** are formed. Although the C-H_b bond energy is less than C-H_a due to its allylic nature, the geometry for elimination of H_a is more favorable. Therefore, finding the right combination of steric and electronic factors present in the starting 1,6-enyne in conjunction with the nature of the transition metal catalyst, either regioisomer can usually be had selectively.

Scheme 1c.21



1.C.6 Transition Metal-Catalyzed Domino Reactions Which Incorporate a Carbocyclization Event

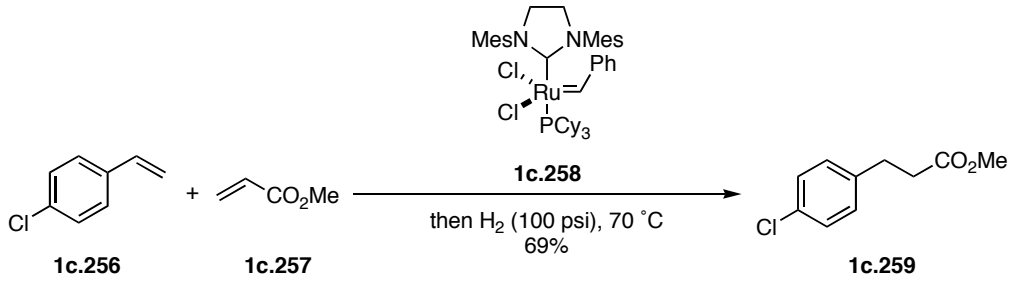
As the field of transition metal-catalyzed reactions expands, the prospect of being able to rapidly assemble structurally complex intermediates from relatively simple

starting materials becomes ever easier. One of the major thrusts in research endeavors by a number of groups recently has been the development of tandem/domino processes in which a number of transformations occur in a single reaction vessel. The variety of reactions amenable to domino processes greatly expands when transition metal-mediated transformations are considered. An increasing amount of attention has been paid recently to developing methods that involve the manifestation of multiple transformations occurring in a single pot mediated by a *single* catalyst. The advent of such processes dramatically increases the efficiency by providing the desired products in a low-cost manner, while keeping the waste generated to a minimum. With the development certain transition metal species capable of catalyzing a number of different reactions, it has become even easier to establish conditions in which combining these transformations to yield a single-pot method resulting in more and more reports surfacing with ever increasing frequency.[288]

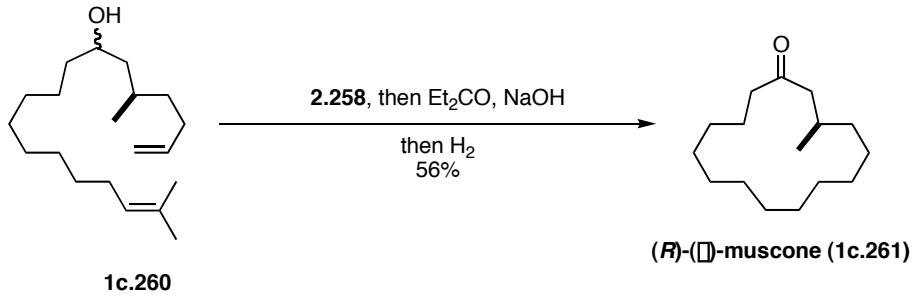
These types of processes can be divided into two categories: sequential and concurrent catalysis. The first type, sequential catalysis, is distinguished by those transformations in which the product of the first reaction serves as the starting material for the second in which the catalytic activity of the metal is moderated by some change in the reaction conditions (*i.e.* temperature change). Alternatively, concurrent reactions are those that occur simultaneously in the same reaction vessel by the same catalyst. This discussion will be limited to addressing the first of these classes, namely the recent advances in sequential catalysis.[288]

Possibly the largest subclass of sequential reactions to provide numerous successful examples in recent years feature the utilization of ruthenium olefin metathesis catalysts, namely those developed by Grubbs and coworkers.[289] These domino processes include at least one of the sequential reactions, usually the first, to be either a ring-closing

metathesis (RCM), cross metathesis, ring-opening metathesis polymerization (ROMP) or an acyclic diene metathesis (ADMET). Oxidation of ketones and the reduction of carbon-carbon double bonds have been shown to be viable reactions in domino processes in which the metathesis event occurs first. For example, a cross metathesis of styrene derivative **1c.256** with **1c.257** was followed by hydrogenation under 100 psi of H_2 to yield methyl ester **1c.259** in 69% yield (Eq. 1c.30).[290] Likewise, initial RCM of diene **1c.260** using Grubbs' second generation catalyst **1c.258** followed by oxidation with 3-pentanone and subsequent hydrogenation yielded (*R*)-(−)-muscone (**1c.261**) in an attractive three-step one-pot sequence (Eq. 1c.31).



(1c.30)

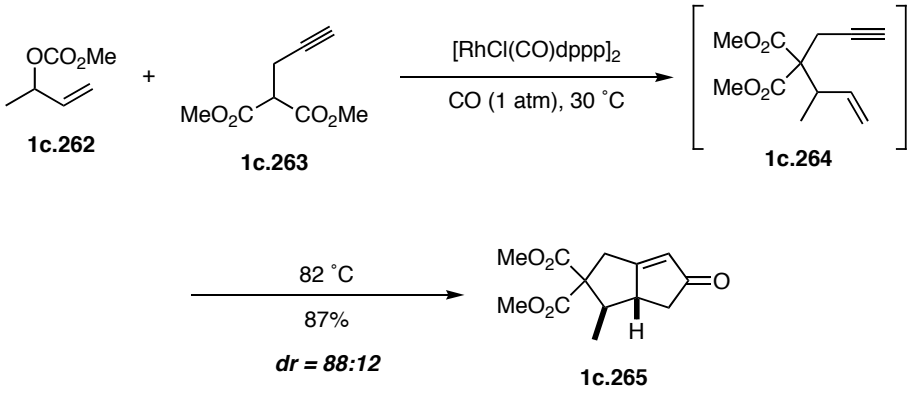


(1c.31)

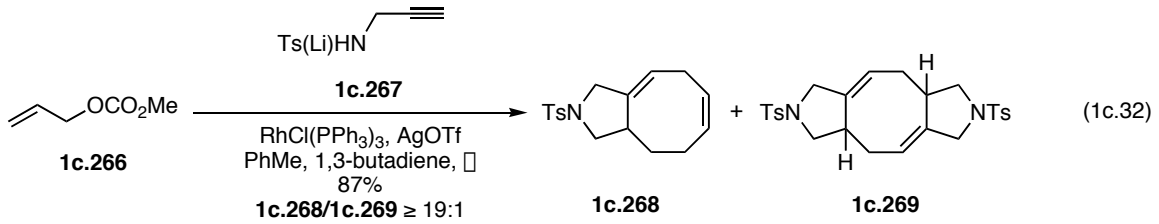
Evans' and coworkers have established a unique regioselective rhodium(I)-catalyzed allylic alkylation reaction to yield products resulting from substitution at the more substituted allylic terminus *vida supra*. The unique regioselectivity of this method was then utilized in conjunction with the ability of the rhodium(I) source to establish

sequential reaction sequences. In 2001 Evans showed that the alkylation of allylic carbonate **1c.262** with alkyne **1c.263** proceeded in the presence of $[RhCl(CO)dppp]_2$ under 1 atm of CO to yield enyne **1c.264** which underwent subsequent Pauson-Khand annulation when the reaction temperature was elevated (room temperature to 82 ˚C) to provide bicyclic enone **1c.265** in 87% yield and a diastereomeric ratio of 88:12 (Scheme 1c.22).[291]

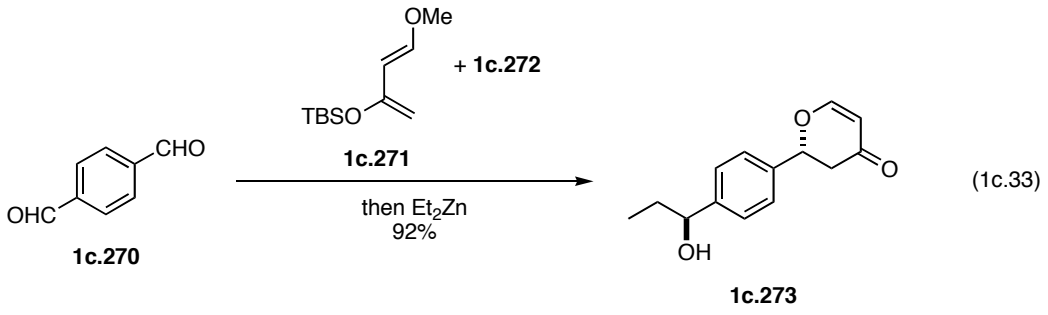
Scheme 1c.22

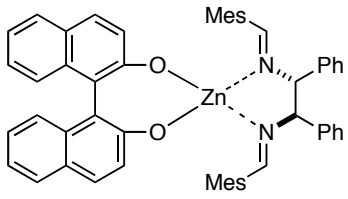


In 2002, Evans' expanded the scope of the rhodium(I)-catalyzed domino allylic alkylation/carbocyclization methodology to include the tandem three-component rhodium(I)-catalyzed allylic alkylation/[4+2+2] cycloaddition reaction. In this carbocyclization event, a diene in solution coordinates to the metallocarbocycle intermediate, undergoes migratory insertion and, following reductive elimination of the rhodium(III) species, provides a [6.3.0] bicyclic diene.[292] As illustrated by Eq. 1c.32, when allylic carbonate **1c.266** was treated the lithium sulfonamide **1c.267** in the presence of $RhCl(PPh_3)_3$/AgOTf and 1,3-butadiene, an excellent yield of cycloadduct **1c.268** was obtained with little homocycloaddition product **1c.269** observed.



The use of zinc catalysts, although less frequent in the processes discussed thus far, have also shown utility in the development of transition metal-catalyzed sequential reactions. In 2003, Du and Ding showed how the chiral zinc catalyst **1c.272** catalyzed the hetero-Diels-Alder cycloaddition of Danishefsky's diene **1c.271** to dialdehyde **1c.275** which upon treatment with diethyl zinc *in situ* provided benzyl alcohol **1c.273** in 92% yield (Eq. 1c.33).[293] Analysis showed that the [4+2] cycloaddition proceeded in 97% *ee* and the subsequent addition of diethyl zinc to the remaining aldehyde went with near complete diastereoselectivity (> 97:3). The chemoselectivity of the process is noteworthy in that the initial cycloadduct was less prone to undergo another hetero-Diels-Alder reaction, thereby allowing for diethyl zinc addition.





1c.272

1.C.7 Overall Summary of Section 1.C

The use of transition metals to catalyze carbocyclization reactions has become an intriguing topic in recent years, leading to a rapid expansion of methods and scope. Utilizing the methods described herein, a number of ring sizes can be formed in very unique ways. Most of these cyclizations are simply not possible without the assistance of a transition metal catalyst in some way or another. The potential to render such reactions enantioselective is one of the more intriguing aspects of this budding area of research. Through the use of chiral ligands and low quantities of reagents necessary (catalytic loadings < 5 mol% in most cases) decreases the amount of waste generated, as well as enhancing the atom economy of such processes. Unfortunately, with the exception of intramolecular cyclopropanations, enantioselective variants of the reactions detailed is this section have not been fully developed to include a wide range of substrates and alternative catalyst systems. With the progress being made to develop tandem/domino sequences, the assembly of complex intermediates becomes ever more rapid, increasing efficiency and throughput. As a result, transition metal-catalyzed processes of these types represent the vanguard of synthetic methodology.

1.D CHAPTER 1 CONCLUSIONS

Transition metal-catalyzed reactions constitute a useful method to rapidly assemble complex molecules, often times by enabling reactions untenable without the assistance of a metal catalyst. Although the metal-catalyzed allylic alkylation of unsymmetric allylic substrates constitutes one of the most widely used transformations in modern synthetic chemistry, it is as of yet not fully developed. Many of the transition metals examined have exhibited limited utility in the allylic alkylations of unsymmetrical substrates with hard nucleophiles. Additionally, the formal direct regiochemical trend

observed in rhodium-catalyzed reactions has not been explored fully, and a reliable method developed.

The second major section of this chapter dealt with those cyclizations that are unlikely or inefficient without the use of a transition metal catalyst. Although there are numerous benefits to their use, particularly in the area of natural product synthesis, there still exists many opportunities to improve upon what has been reported. As mentioned earlier, many of these reactions have not been developed into a reliable enantioselective transformation, glaringly absent considering the present focus on asymmetric transformations. The intramolecular [5+2] cycloaddition, although extremely diastereoselective, relies on the enantiopurity of the starting enynes for asymmetry. Therefore, it would be advantageous if a method were developed that allowed a rapid assembly of chiral starting materials for the [5+2] cycloaddition. Possibly synthesizing the starting cyclopropylenynes utilizing a short sequence starting with an asymmetric cyclopropanation? A method such as this would use one efficient transition metal-catalyzed carbocyclization to lead into another for the rapid assembly of complex intermediates. The other transformations introduced, the Pauson-Khand annulation and enyne cycloisomerization, have been used in natural product synthesis, but recent endeavors have focused on incorporating these reactions into domino sequences. These aspects, in conjunction with the unique functionality of the compounds assembled in this manner allow for the potential development of domino reactions to optimize reaction efficiency and process throughput.

Although a vast amount of work has been accomplished with regards to studying transition metal-catalyzed reactions, there still exists the potential to improve upon what has been reported. As one might expect, with each new development in the field, presumably answering a crucial scientific question, another dilemma is uncovered.

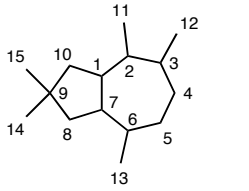
Future endeavors will most certainly focus on further development of asymmetric variants and designing novel and more efficient domino sequences. Hopefully, this chapter has laid the framework for understanding the concepts of a sampling of transition metal catalysis while causing the reader to ask how improvements can be made on existing methodology.

Chapter 2. Enantioselective Total Synthesis of Tremulenediol A and Tremulenolide A

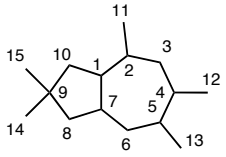
2.1 INTRODUCTION

The tremulanes constitute a novel class of sesquiterpene natural metabolites containing a unique carboskeletal array.[294] The carbon skeleton of the tremulanes **2.1** is isomeric to the lactarane skeleton (**2.2**) and similar in structure to some particularly intriguing terpenes such as guanecastapene (Figure 2.1).[295] Tremulenolide A (**2.3**) and tremulenediol A (**2.4**) are two representative tremulanes that were isolated in 1993 from the fungal pathogen *Phellinus tremulae* as part of a project to develop methods for controlling fungal decay and staining in trembling or quaking aspen (*Populus tremuloides*).[294] Aspen represents 11% of the entire Canadian timber resource and 54% of the net merchantable hardwood timber. *P. tremulae*, the most serious wood rotting pathogen of aspen in Canada, greatly reduces the potential economic value of this timber reserve. Although the commercial advantages associated with the potential biological activity that these two natural products may possess is intriguing in itself, the interesting structural aspects of their skeletal core was the primary reason for choosing **2.3** and **2.4** as synthetic targets. Most notably, the 2,3,6,9-substitution pattern around the [5.3.0] bicyclic carbon skeleton and the relative configurations of the three stereogenic centers around the 7-membered ring caught our attention as being well suited for the application of synthetic methodology recently developed in our research group. The goal was to establish an atom economical, convergent enantioselective approach to the tremulanes by assembling them in manner that showcased the synthetic methodology developed in the Martin research group.

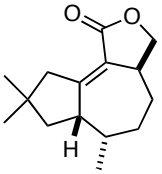
Figure 2.1. Tremulane Sesquiterpenes and Related Natural Products



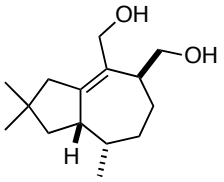
Tremulane Carbon Skeleton (**2.1**)



Lactarane Carbon Skeleton (**2.2**)



Tremulenolide A (**2.3**)

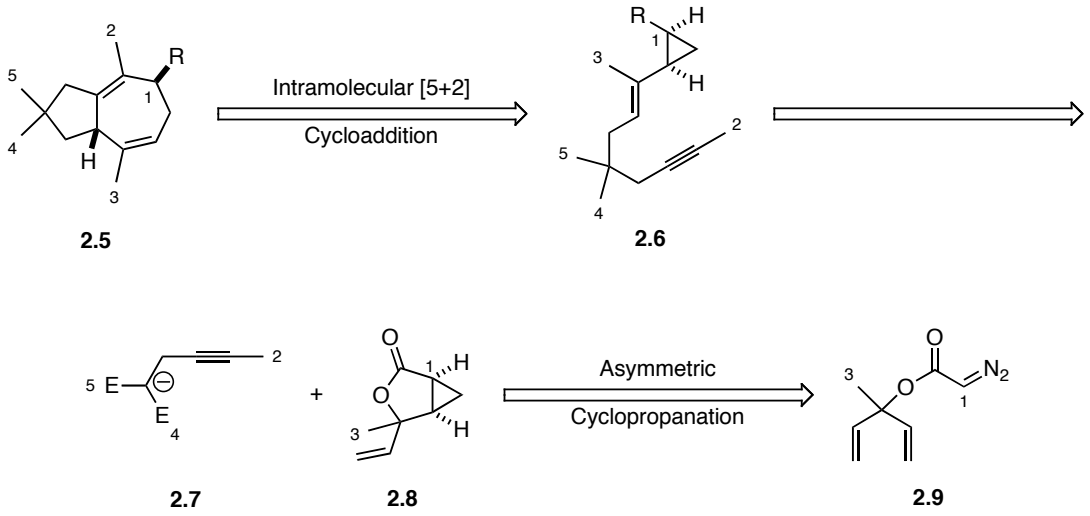


Tremulenediol A (**2.4**)

Tremulenolide A and tremulenediol A were chosen as synthetic targets to illustrate how the intramolecular rhodium(II)-catalyzed enantioselective cyclopropanation strategy,[191] which was developed in our research group over the last decade, can be used to set the stage for a diastereoselective intramolecular rhodium(I)-catalyzed [5+2] cycloaddition[235] as an efficient entry into the tremulane carbon skeleton. As illustrated in Scheme 2.1, this approach establishes the absolute configuration of the C-3 stereocenter in cycloadduct **2.5** from the asymmetric cyclopropanation of diazoester **2.9** to provide cyclopropyl lactone **2.8**. Construction of the C-7 stereogenic center in **2.5** arises as a consequence of the diastereoselectivity inherent to the intramolecular [5+2] cycloaddition. Subsequent diastereoselective reactions allow for the formation of the C-6 stereocenter in the tremulane natural products. The proposed route is highly convergent as each carbon in the [5.3.0] bicycle, as well as all five substituents, are introduced by the

union of alkyne **2.7** and lactone **2.8** to provide enyne **2.6**. To date, an enantioselective synthesis of **2.3** or **2.4** has not been reported although Davies revealed a synthesis of the racemic compounds in 1998 utilizing a tandem intramolecular cyclopropanation/Cope rearrangement strategy; this is the only reported approach to these two natural products.[296]

Scheme 2.1



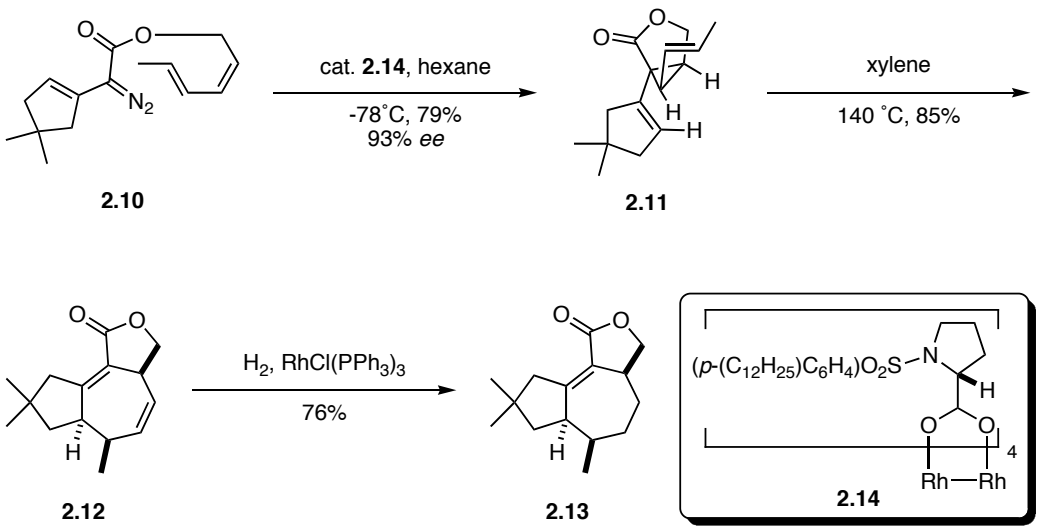
2.5 **2.6** **2.7** **2.8** **2.9**

2.2 DAVIES' TOTAL SYNTHESIS OF TREMULENOLIDE A AND TREMULENEDIOL A

Davies was the first to report in 1998 a synthetic approach toward members of the tremulane sesquiterpene metabolites.[296] The focal point of their synthetic approach was the use of a cyclopropanation/rearrangement strategy involving a vinylcarbenoid and diene to prepare stereoselectively seven-membered ring analogs.[297] This method was introduced in 1994 as a unique [3+4] annulation strategy that could be rendered enantioselective with the use of chiral ligands in the initial cyclopropanation reaction.[298] As illustrated in Scheme 2.2, diazodecomposition of **2.10** by the chiral prolinate dirhodium(II) catalyst **2.14** leads to an asymmetric cyclopropanation of the *cis* double

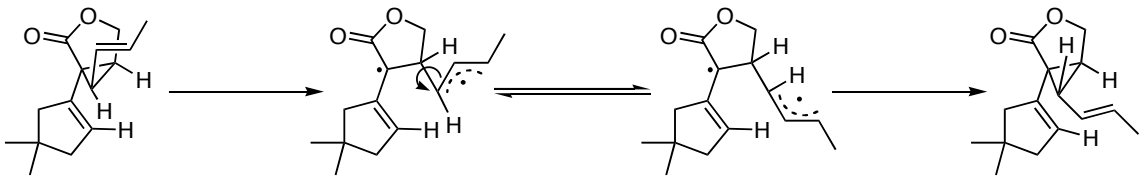
bond nearest the tether to provide *trans*-divinylcyclopropane **2.11**. Lactone **2.11** underwent smooth Cope rearrangement upon heating in refluxing xylenes to yield the tremulane skeleton **2.12**. Subsequent catalytic hydrogenation of **2.12** with Wilkinson's catalyst provided the tremulane carbon skeleton **2.13** in 76% yield.

Scheme 2.2



The authors speculated that **2.12** was formed by equilibration first to the corresponding *cis*-divinylcyclopropane to satisfy the geometrical requirements for the Cope rearrangement. As illustrated in Scheme 2.3, this thermally induced isomerization process is thought to proceed through the diradical intermediate **2.15**.[299] Initial cleavage yields intermediate **2.15a** that, following bond rotation as indicated, proceeds through intermediate **2.15b** to reform the cyclopropane ring and give the *cis*-divinyl isomer **2.16**. The overall transformation was amended to a tandem process by heating the reaction mixture following the initial rhodium(II) prolinate-catalyzed cyclopropanation of diazoester **2.10**. Davies' proposed that this sequence would provide a rapid, enantioselective entry into the skeletal cores of tremulenolide A and tremulenediol A.

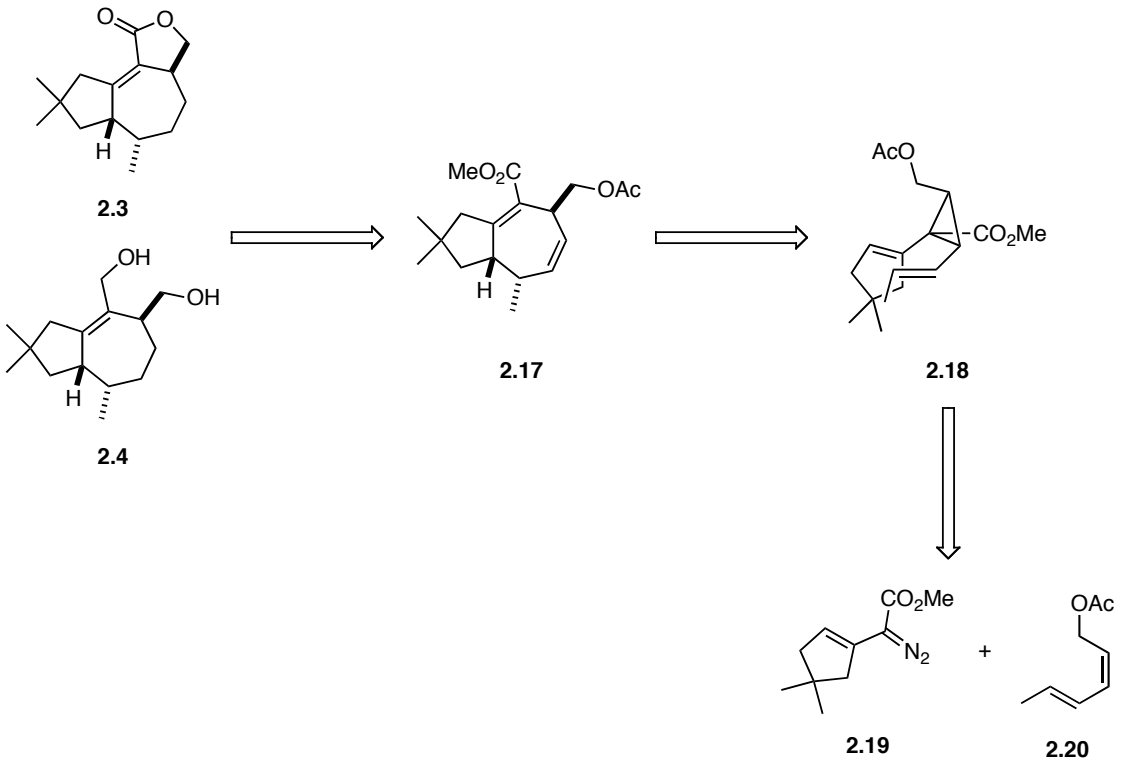
Scheme 2.3



2.11 **2.15a** **2.15b** **2.16**

The retrosynthetic outline Davies' used to assemble these two natural products is illustrated in Scheme 2.4. Both tremulenolide A and tremulenediol A would be obtained from a common intermediate **2.17** that contains the complete tremulane carbon skeletal framework with all three stereocenters in the correct relative configuration. Intermediate **2.17** arises from an intermolecular tandem cyclopropanation/Cope rearrangement of diazoester **2.19** and diene **2.20** through the unisolated intermediate divinyl cyclopropane **2.18**. This approach does an excellent job of highlighting the regio- and stereoselectivity associated with intermolecular vinylcarbenoid cyclopropanations of diazoesters with dienes to form *cis*-divinylcyclopropanes.[300] However, the success of this approach relies on being able to control the relative stereochemistry of the three stereogenic centers. Fortunately, the stereoselectivity arises as a result of the boat transition state required in the subsequent Cope rearrangement of intermediate **2.18**.[301]

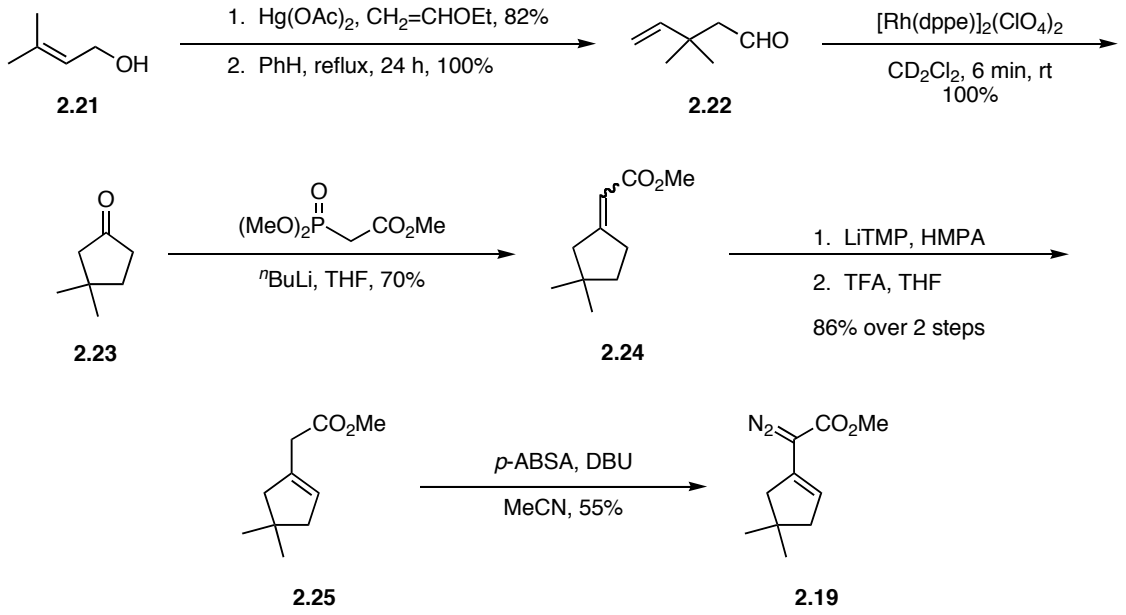
Scheme 2.4



Davies' synthesis of **2.3** and **2.4** began with the synthesis diazoester **2.19** in a four-step sequence from known cyclopentanone **2.23** (Scheme 2.5). Ketone **2.23** was obtained in three steps from allylic alcohol **2.21** as reported independently by Boeckman[302] and Bosnich.[303] Mercury-catalyzed vinylation[296] of **2.12** followed by Claisen rearrangement[304] of the resulting allyl vinyl ether provided aldehyde **2.22** in 82% overall yield. Rhodium-catalyzed hydroacylation of aldehyde **2.22** yielded cyclopentanone **2.23** in excellent yield.[303] Subsequent Horner-Emmons olefination of ketone **2.23** followed by deconjugation of the resulting □,□-unsaturated ester **2.24** with LiTMP and TFA regioselectively provided □,□-unsaturated ester **2.25** in 60% overall yield (contaminated with ~5% of the other possible olefinic regioisomer). Diazo transfer utilizing *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) in the presence of DBU provided

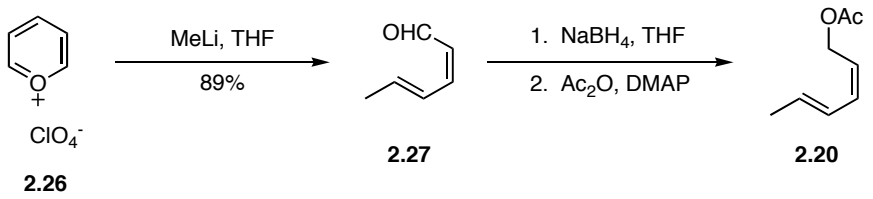
ester **2.19** in 55% yield from **2.23**. The authors reported that *p*-ABSA was chosen as the diazo transfer reagent due to better yields, greater ease of handling and the amide byproduct is easily removed in the work up as compared to typical reagents such as *p*-toluenesulfonyl azide.

Scheme 2.5



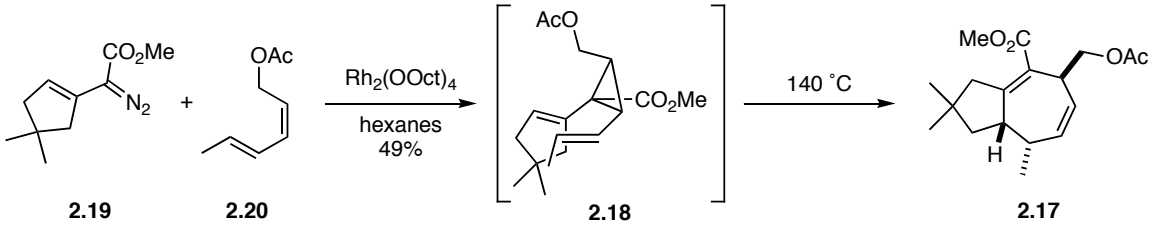
The diene component **2.20** was obtained in a three-step sequence from pyrylium perchlorate, which was synthesized in two steps from commercially available pyridine and sulfuryl chloride.[305] Treatment of **2.26** with methyllithium resulted in regioselective addition to C-2, and subsequent heating of the reaction mixture initiated a rearrangement that provided aldehyde **2.27** in >95% stereochemical purity and 89% yield. Borohydride reduction of **2.27** and acylation of the resulting primary alcohol yielded allylic acetate **2.20**.[306]

Scheme 2.6



Rhodium(II)-catalyzed diazodecomposition of **2.19** in refluxing hexanes and in the presence of a 12-fold excess of diene **2.20** initially provided a mixture of the desired product **2.17** and *cis*-divinylcyclopropane **2.18** (Scheme 2.7). In order to induce the Cope rearrangement, forcing conditions were necessary to overcome the high energy of activation associated with the crowded boat transition state. Thus, when excess diene **2.20** was removed from the crude mixture of **2.17** and **2.18** by Kugelrohr distillation under vacuum at 60 ˚C and subsequent heating of the distillation apparatus to 140 ˚C, *cis*-divinylcyclopropane **2.18** underwent Cope rearrangement to provide the desired cycloadduct **2.17** as the sole regioisomer in 49% yield.

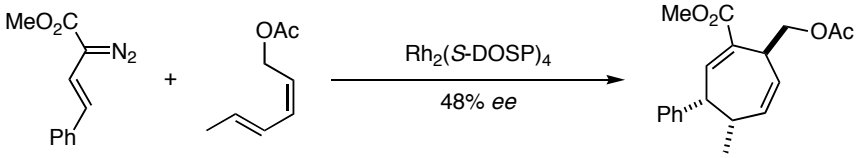
Scheme 2.7



Davies next examined an asymmetric approach to bicycle **2.17** in which the tandem cyclopropanation/Cope rearrangement sequence would be rendered enantioselective through the use of the chiral prolinate catalyst, Rh_2[(*S*)-DOSP]$_4$. This catalyst was chosen based on Davies' previous report illustrating the use of Rh_2[(*S*)-

DOSP]$_4$ as an effective catalyst for the enantioselective cyclopropanation of olefins with vinylcarbenoids.[160] Unfortunately, when the intermolecular cyclopropanation of **2.20** with **2.19** was conducted in the presence of Rh_2[(*S*)-DOSP]$_4$, subsequent heating to initiate the Cope rearrangement provided cycloheptadiene **2.17** in a disappointing 4% *ee*. To determine whether the poor facial selectivity was due to the vinylcarbenoid or the diene, the test reactions depicted in Eqs. 2.1 and 2.2 were performed. The good enantioselectivity observed in the cyclopropanation of diazoester **2.17** with styrene (**2.28**) in the presence of Rh_2[(*S*)-DOSP]$_4$ suggests that the cyclopropanation reaction proceeds with good facial selectivity (Eq. 2.1). However, when diazoester **2.30** was treated with diene **2.20** and Rh_2[(*S*)-DOSP]$_4$, the resulting cycloheptadiene **2.31** was obtained in only 48% *ee* (Eq. 2.2). Given that cyclopropanations of **2.30** with a number of other dienes,[307] including styrene,[160] proceeded with excellent enantioselectivities (98% *ee* as reported with styrene at -78 ˚C), the authors surmised that the low enantioselectivity was most likely the result of poor facial selectivity associated with the diene **2.20** and not the carbenoid resulting from **2.19**.

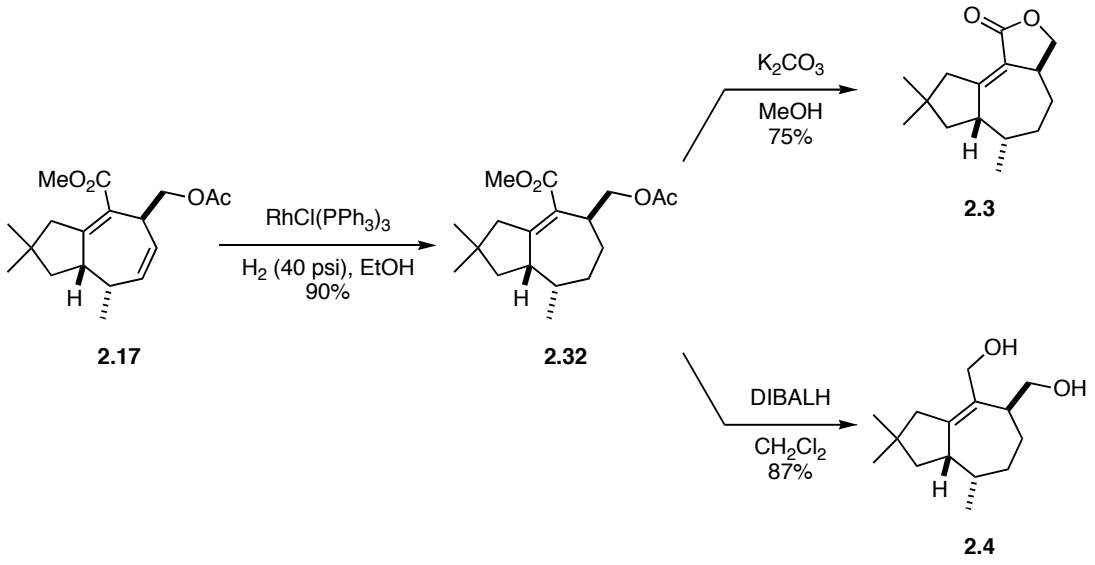
2.19 **2.28** **2.29** (2.1)



2.30 **2.20** **2.31** (2.2)

Given the lack of success at rendering the key cyclopropanation/Cope rearrangement step enantioselective, Davies pursued the synthesis of racemic tremulenediol A and tremulenolide A (Scheme 2.8). Catalytic hydrogenation of **2.17** with Wilkinson's catalyst under an atmosphere of 40 psi of H_2, reduced the disubstituted olefin leaving the tetrasubstituted double bond intact to yield intermediate **2.32** in 90% yield. One salient feature of this route is that intermediate **2.32** represents a branching point where one can pursue either tremulenolide A or tremulenediol A. To that end, saponification of both esters in **2.32** with potassium carbonate in MeOH followed by *in situ* lactonization provided **2.3** in 75% yield. Alternatively, reduction of diester **2.32** with excess DIBALH in CH_2Cl_2 at -78 ˚C gave tremulenediol A in 87% yield.

Scheme 2.8



Thus, Davies showed how the tandem cyclopropanation/Cope rearrangement strategy developed in his laboratories provided an efficient, stereoselective entry into the tremulane carbon skeleton, as illustrated by the syntheses of racemic tremulenolide A and tremulenediol A. The synthetic route required 16 total steps from commercially available

starting materials, and was completed in an overall yield of 0.8% for **3.3** and 0.9% for **3.4**. The approach highlights the exceptional level of stereoselectivity in the tandem process to assemble three stereogenic centers in a single transformation. Unfortunately, due to problems associated with alkene facial selectivity in the intermolecular cyclopropanation of diene **2.20** with diazoester **2.19**, the use of a chiral dirhodium(II) catalyst failed to provide the desired [5.3.0] bicycle enantioselectively.

2.3 1ST GENERATION STRATEGY TOWARD THE TOTAL SYNTHESIS OF TREMULENOLIDE A AND TREMULENEDIOL A

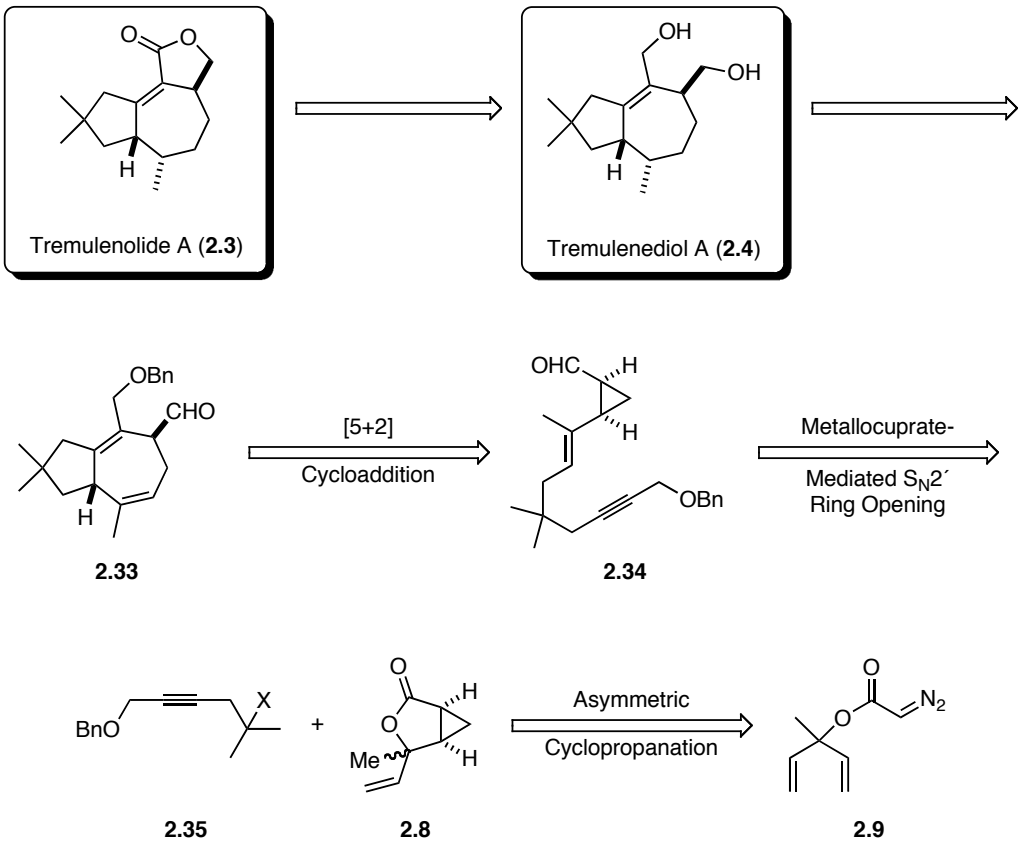
The tremulanes provide a unique opportunity to explore new techniques for the synthesis of carbocyclic natural products. The substitution pattern coupled with the relative configuration of each stereogenic center make this class of metabolites attractive synthetic targets. Upon analysis of tremulenolide A and tremulenediol A, we were immediately drawn to the construction of the [5.3.0] bicyclic core, which we envisioned to arise as a result of a transition metal catalyzed [5+2] cycloaddition reaction of an appropriately functionalized, enantioenriched cyclopropyl enyne. With this disconnection in mind, the opportunity presented itself to utilize the rhodium(II)-catalyzed asymmetric cyclopropanation methodology developed in our group to establish the first asymmetric synthesis of **2.3** and **2.4**.

The chiral carboxamide dirhodium(II)-catalyzed enantioselective cyclopropanation methodology described in Chapter 1 has been used for the synthesis of enantioenriched, conformationally constrained peptide analogs to study protein-ligand interactions.[308] The recent total synthesis of ambruticin by Martin and coworkers establishes a benchmark in utilizing this method for the construction of complex natural products.[309] The focus of the present project was to illustrate the synthetic utility of the

enantioselective cyclopropanation as the entry point for a diastereoselective intramolecular [5+2] cycloaddition leading to the synthesis of tremulane natural products. Thus, we engaged in studies directed toward the first enantioselective total synthesis of tremulenolide A (**2.3**) and tremulenediol A (**2.4**).

Our first generation approach toward these tremulane sesquiterpenes is illustrated in Scheme 2.9. We envisioned that tremulenolide A would arise from the allylic oxidation of the diol moiety present in tremulenolide A that in turn would be synthesized through a series of standard functional group manipulations from intermediate **2.33**. The substituted [5.3.0] bicyclic carbon skeleton in **2.33** would be formed from a diastereoselective rhodium(I)-catalyzed intramolecular [5+2] cycloaddition of the cyclopropyl enyne **2.34**. Utilizing an organocuprate reagent derived from alkyl halide **2.35** to facilitate an S_N2' ring opening of lactone **2.8** followed by reduction of the resulting carboxylic acid moiety yields enyne **2.34**. The aldehyde **2.34** contains all the carbon atoms present in **2.3** and **2.4**, thereby illustrating the convergency and efficient aspects of the proposed route. Cyclopropyl lactone **2.8** was envisioned to arise from the enantioselective, intramolecular rhodium(II)-catalyzed cyclopropanation of diazoester **2.9**.

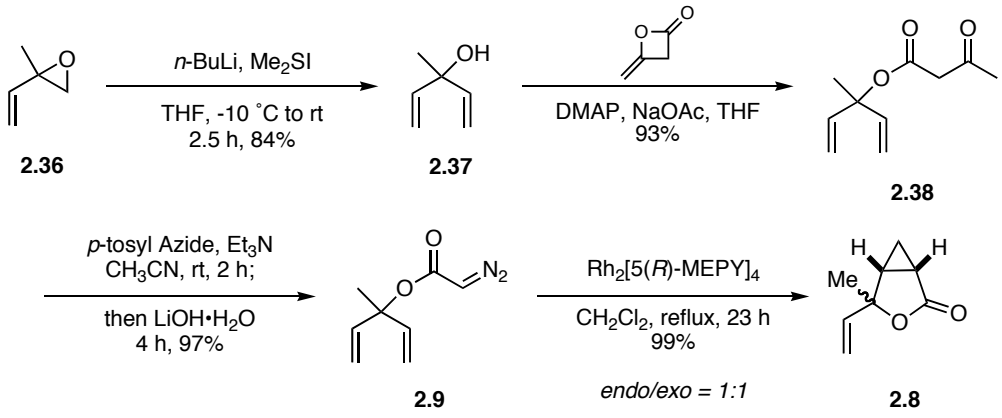
Scheme 2.9



Based on this strategy, we commenced our efforts with the enantioselective construction of cyclopropyl lactone **2.8** in a straightforward four-step approach from commercially available 2-methyl-2-vinyl oxirane **2.36** (Scheme 2.10). Thus, treatment of oxirane **2.36** with the sulfur ylide of trimethylsulfonium iodide followed by an *in situ* -elimination of dimethylsulfide provided divinyl carbinol **2.37** in 84% yield.[310] In order to circumvent the use of expensive reagents at this early stage, we briefly explored an alternative method in which alcohol **2.36** could be obtained by the addition of excess vinyl magnesium bromide to ethyl acetate. Unfortunately, this process was extremely unreliable, often providing the desired carbinol in less than 20% yield. Subsequent

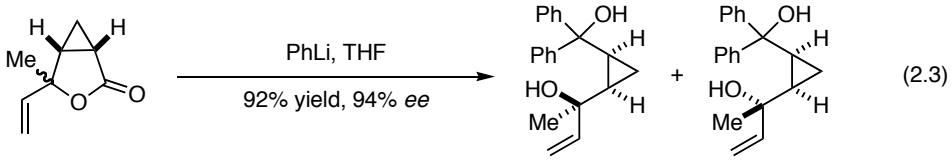
acylation of **2.37** with diketene in the presence of 4-dimethylaminopyridine (DMAP) and sodium acetate provided acetoacetate **2.38** in 93% yield. A one-pot diazo transfer reaction of **2.38** with *p*-toluenesulfonyl azide (*p*-TsN_3) and Et_3N, followed by hydrolytic cleavage of the ketone functionality with $LiOH•H_2O$ provided diazoester **2.9** in an optimized 97% overall yield. This process proved extremely difficult to optimize, as the facility with which diazoester **2.9** decomposed was quite astounding. Under even the most mildly acidic conditions led to extensive decomposition of **2.9** from which no amount of desired product could be extracted. Application of the Corey-Myers diazoesterification procedure[311] to carbinol **2.37** was also problematic. The sterically hindered tertiary alcohol was extremely resistant to acylation with anything but a highly activated carbonyl moiety.

Scheme 2.10



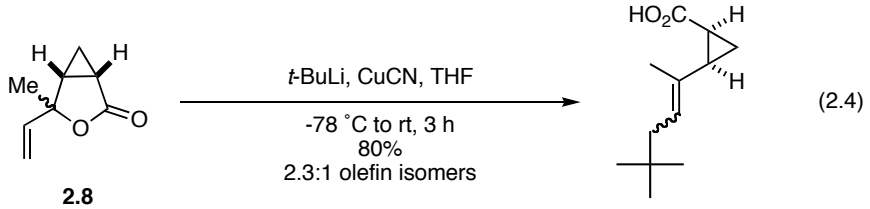
When the diazoester **2.9** was exposed to 0.1 mol% of $Rh_2[5(R)\text{-MEPY}]_4$ intramolecular cyclopropanation proceeded smoothly to yield the desired cyclopropyl lactone **2.8** as a mixture (1:1) of C4 epimers in 99% yield and 94% *ee* for each disatereomer.[191,312] The enantioselectivity of the cyclopropanation reaction was determined by treating the diastereomeric mixture of cyclopropyl lactones **2.8** with

phenyllithium in THF to yield diols **2.39a** and **2.39b** (Eq. 2.3). Subsequent analytical chiral HPLC analysis of each diastereomeric ketone provided the enantiomeric excess from the cyclopropanation of diazoester **2.9** with $Rh_2[5(R)\text{-MEPY}]_4$. That a mixture of cyclopropyl lactones was obtained in the cyclopropanation is inconsequential due to the destruction of the epimeric center in the next step of the synthesis. Gratifyingly, this optimized sequence provided the desired cyclopropyl lactone **2.8** in 71% overall yield over four steps.



2.8 **2.39a** **2.39b** (2.3)

In an effort to examine the feasibility of the proposed organocuprate mediated S_N2' ring opening reaction, cyclopropyl lactone **2.8** was treated with the tertiary cuprate reagent derived from *t*-BuLi and CuCN (Eq. 2.4).[313] To our delight, the desired vinyl cyclopropane **2.40** was obtained in 80% yield as a mixture (2.3:1) of olefinic isomers. Confident that the organocuprate reagent derived from alkyne **2.35** would add in a regioselective fashion to cyclopropyl lactone **2.8** to provide the desired cyclopropyl enyne, we turned our attention toward the difficult task of synthesizing the homopropargylic tertiary halide **2.35**.

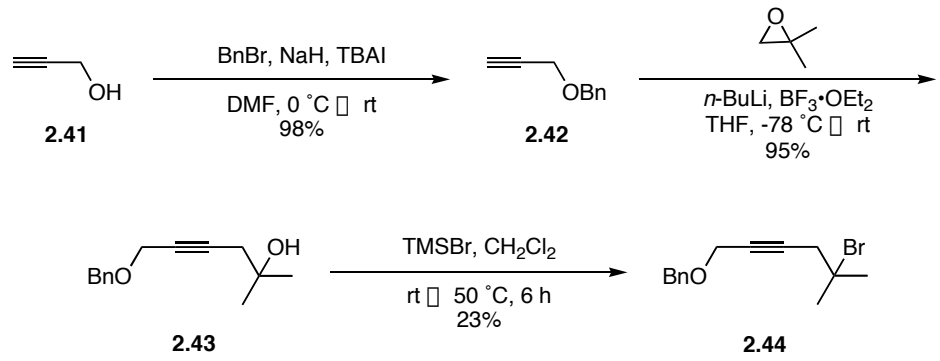


2.8 **2.40** (2.4)

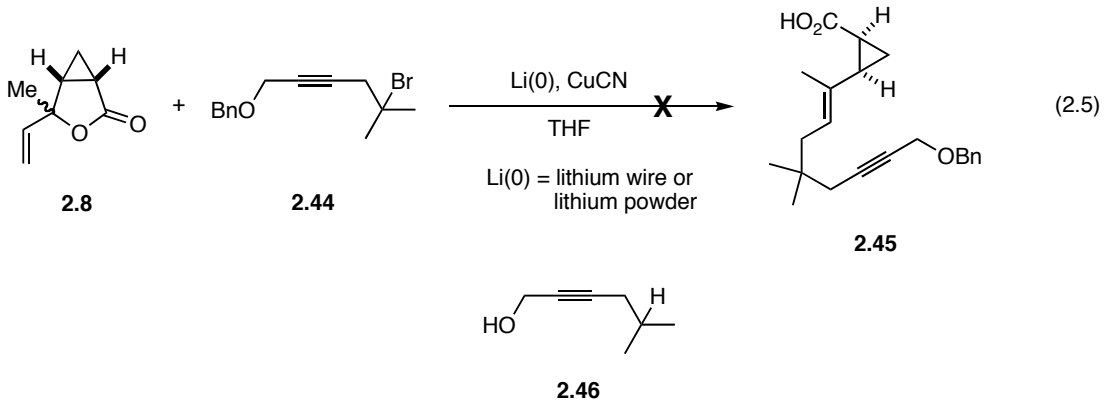
We originally envisioned that halide **2.35** could be synthesized directly from the corresponding tertiary alcohol. Toward this end, homopropargylic tertiary alcohol **2.43** was synthesized in a high yielding, two step sequence as illustrated in Scheme 2.11. First, propargyl alcohol (**2.41**) was treated with BnBr and NaH in the presence of TBAI to yield benzyl ether **2.42** in 98% yield.[314] The benzyl protecting group was chosen at this stage to allow for its concomitant removal along with catalytic hydrogenation of the trisubstituted olefin present in the advanced bicyclic intermediate **2.33** *en route* to tremulenediol A.

With alkyne **2.42** in hand, the lithium acetylide was generated by addition of *n*-BuLi and treated with isobutylene oxide in the presence of BF_3•OEt_2 to provide the tertiary alcohol **2.43** in 95% yield.[315] Unfortunately, conversion of alcohol **2.43** to the corresponding bromide **2.44** proved to be anything but straightforward. After considerable experimentation, the conversion was effected with TMSBr in CH_2Cl_2; however, this reaction proceeded in a paltry 23% yield.[316] A plethora of bromination conditions were screened, including, but not limited to, PBr_3, PBr_3 and pyridine, and TMSCl and LiBr. Unfortunately, none of these conditions improved upon the results obtained with TMSBr. The lack of success experienced in this transformation may be due to the apparent instability of the resulting homopropargylic, tertiary bromide, the formation of elimination side products or the migratory aptitude of the intermediate tertiary carbocation.

Scheme 2.11



With limited quantities of tertiary alkyl bromide **2.44** in hand, we turned our attention toward coupling the derived organocuprate with cyclopropyl lactone **2.8**. Unfortunately, metallation of **2.44** proved difficult as might be expected of a tertiary homopropargylic halide. Attempts to effect metal-halogen exchange using either lithium wire or lithium powder, followed by transmetallation with CuCN and subsequent treatment with lactone **2.8** led to none of the desired cyclopropyl enyne **2.45** (Eq. 2.5). In each case, lactone **2.8** was recovered from the reaction mixture intact. Additionally, when lithium wire was used in excess, the reduced, deprotected propargylic alcohol **2.46** was obtained. Formation of the lithium alkoxide upon benzyl group deprotection may be playing an inhibitory role in obtaining a quantitative metallation, or interfere with the resulting nucleophilic addition to lactone **2.8**. However, the exact nature of any potential interference arising from the formation of **2.46** is purely speculative at this juncture. Therefore, we turned our attention toward reexamining our protecting group strategy to prepare a substrate that would be stable to the metallation conditions.

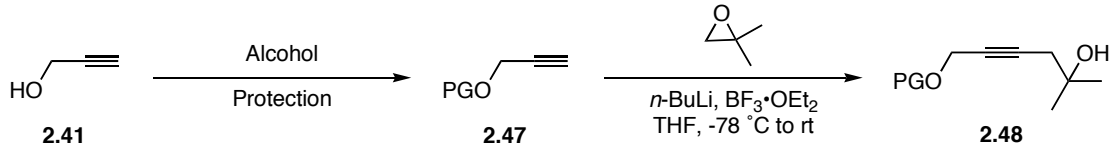


A number of propargylic alcohols of type **2.47** with different hydroxyl protecting groups were considered as potential substrates. The caveat in choosing the protecting group was finding one that was not only stable to the metal-halogen exchange conditions, but also the acidic conditions required for forming the tertiary bromide. Additionally, the optimal protecting group would provide the necessary tertiary alkyl halide in better yield than what was obtained for bromide **3.37** and resist deprotection under the metallation conditions.

Based upon these considerations, the series of propargyl alcohol protected substrates chosen were prepared as illustrated in Table 2.1. For our purposes, methyl propargyl ether **2.47a** would be a particularly robust substrate (entry 1). However, the difficulty associated with removal of the methyl ether as a late-stage synthetic operation would make this protecting group undesirable, and it was therefore chosen simply as a model to investigate metallation conditions. The TIPS-protected[317] alcohol **2.47b** and the TBDPS-protected[318,319] substrate **2.47c** were chosen for their anticipated stability to the metal-halogen exchange conditions and ease of removal at a later stage. Both silyl protecting groups were installed by treating alcohol **2.41** with the corresponding silyl chloride in excellent yields (entries 2 and 3). Finally, methoxy methyl (MOM)

etherification was performed using $CH_2(OMe)_2$ and TfOH to provide **2.47d** in 97% yield (entry 4).[320,321] Treatment of protected alcohol **2.47** with ^{n}BuLi followed by isobutylene oxide and BF_3•OEt_2 provided the homopropargylic alcohols **2.48a-d** in excellent yields.

Table 2.1. Protecting Groups Analyzed for Propargyl Alcohol (**2.41**)

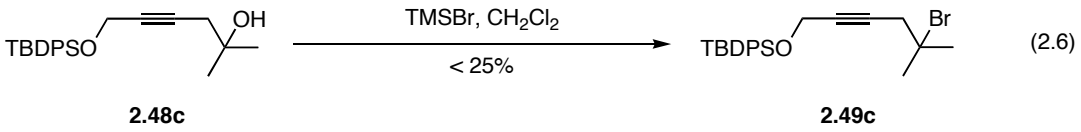


2.41 **2.47** **2.48**

Entry	*Protected Alcohol* **2.47**	*Protecting Group*	*Protection Conditions*	*Yield (%) of* **2.47**	*Yield (%) of 2.48*
1	**2.47a**	Me	–	–	96
2	**2.47b**	TIPS	TIPSCl, imid., DMF	94	99
3	**2.47c**	TBDPS	TBDPSCl, imid. DMF	97	100
4	**2.47d**	MOM	$CH_2(OMe)_2$, TfOH CH_2Cl_2	89	97

With tertiary alcohols **2.48a-d** in hand, a variety of bromination conditions were analyzed.[316,322] To our disappointment, each substrate gave results similar to those which were observed with benzyl ether **2.44**. Bromination reagents PBr_3, TMSBr, and TMSCl/LiBr provided the most promising results with TBDPS-protected substrate **2.48c** (Eq. 2.6). However, yields of **2.49c** under these conditions did not exceed 25%. Bromination of the TIPS- and MOM-protected ethers **2.48b** and **2.48d** gave either

deprotected alcohol or products that were not characterized. Equally disappointing was the observation that attempts to brominate the methyl-protected substrate **2.48a** led in either to decomposition or recovered starting material.

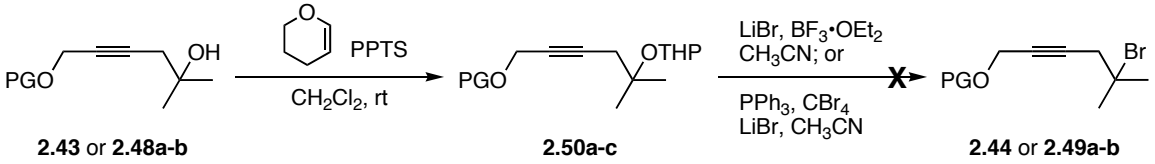


2.48c **2.49c** (2.6)

Unsatisfactory results obtained with: PBr_3, Et_2O; PPh_3, Br_2, pyr., CH_2Cl_2; TMSCl, LiBr, CH_3CN; BBr_3, CH_2Cl_2; BF_3•OEt_2, NaBr, CH_3CN; PPh_3, CBr_4, Et_2O

Mioskowski[323] and Vankar[324] reported independently that tertiary THP ethers could be converted to the corresponding alkyl bromides by treatment with either BF_3•OEt_2 or PPh_3 and CBr_4 followed by LiBr. Under these conditions tertiary THP ethers are readily ionized under relatively mild bromination conditions to form their respective carbocations, which are then trapped by the bromide source. Thus, THP ethers **2.50a-c** were synthesized in excellent yields from the corresponding tertiary alcohols **2.43** and **2.48a-b** by treatment with dihydropyran in the presence of pyridinium *p*-toluenesulfonate (PPTS) (Table 3.2).[325] However, when these THP ethers were treated with either a combination of LiBr and BF_3•OEt_2[324] or PPh_3, CBr_4 and LiBr[323] the tertiary bromides **2.44** and **2.49a-b** were not obtained. It is conceivable that the difficulties encountered may have been due to the potential for □-elimination of the THP ether moiety facilitated by the homopropargylic nature of the substrates analyzed. However, this hypothesis cannot be corroborated at this time due to our inability to isolate the conjugated elimination product.

Table 2.2. Bromination Attempts from the Corresponding Tertiary Bromide



2.43 or **2.48a-b** **2.50a-c** **2.44** or **2.49a-b**

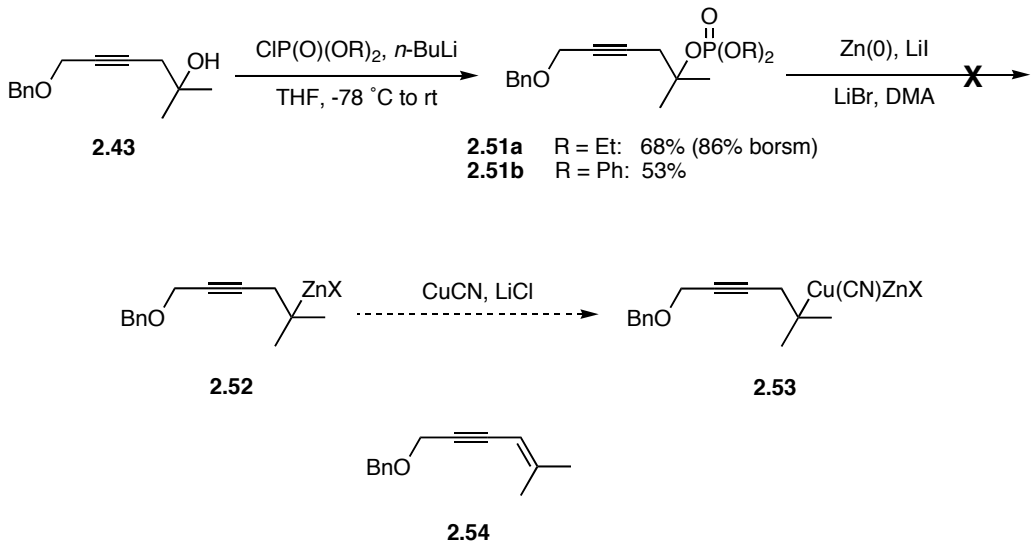
Entry	*Substrate*	*Protecting Group*	*Yield (%) of 2.50*
1	**3.36**	Bn	99
2	**3.41a**	Me	76
3	**3.41b**	TIPS	96

Not entirely discouraged by the difficulties encountered in synthesizing the tertiary organocuprate reagent derived from **2.44**, we surveyed the literature and discovered a few other methods for generating tertiary anions. Knochel showed in 1992 that organozinc compounds could be obtained by treating the corresponding organophosphate with zinc dust.[326] Subsequent transmetallation of the organozinc reagent with CuCN•LiCl served as an efficient way in which highly functionalized organocuprate reagents could be synthesized and used as nucleophiles in conjugate additions. Encouraged by Knochel's work, both diethyl and diphenyl phosphates **2.51a** and **2.51b** were synthesized by treating the tertiary alcohol **2.43** with the dialkyl chlorophosphate and *n*-BuLi in 68% and 53% yield, respectively (Scheme 2.11).[327]

Unfortunately, treatment of either tertiary phosphate **2.51a** or **2.51b** with LiI, LiBr and zinc dust in DMA as described by Knochel and coworkers failed to provide the organozinc compound **2.52**. Extended reaction times and elevated temperatures resulted primarily in thermal □-elimination of the organophosphate functionality to yield a side

product whose ^{1}H NMR was consistent with the conjugated alkyne **2.54**. We speculated that the inability to perform the desired metallation with zinc dust in these experiments may have been due to difficulties associated with Zn(0) activation. A variety of techniques were employed to activate the zinc dust, including treatment with TMSCl and dibromoethane and purification by washing the metal with a solution of inorganic acid. Unfortunately, all efforts to form an organozinc were ineffective. Given the lack of success with zinc dust as a source of Zn(0), we turned our attention toward examining the more reactive Rieke zinc reagent as the source of Zn(0). Once again, tertiary phosphates **2.51a** and **2.51b** proved resistant to metallation, undergoing elimination or decomposition preferentially.

Scheme 2.11



2.43

2.51a R = Et: 68% (86% borsm)
2.51b R = Ph: 53%

2.52

2.53

2.54

At this point it was rapidly becoming apparent that introducing the *gem*-dimethyl moiety directly at this early stage in the synthesis of cyclopropyl enyne **2.34** was not going to work. The lack of success encountered at generating homopropargylic tertiary organocopper species for the coupling reaction was not entirely surprising. There is little

literature support for the metallation of tertiary sp^3 centers, likely owing to the instability of the resulting carbanions. Therefore, an approach that utilized a stabilized carbanion in assembling the [5+2] cycloaddition substrate, we envisioned to simplify the route toward the two tremulanes.

2.4 2ND GENERATION APPROACH INVOLVING A TRANSITION METAL-CATALYZED ALLYLIC ALKYLATION

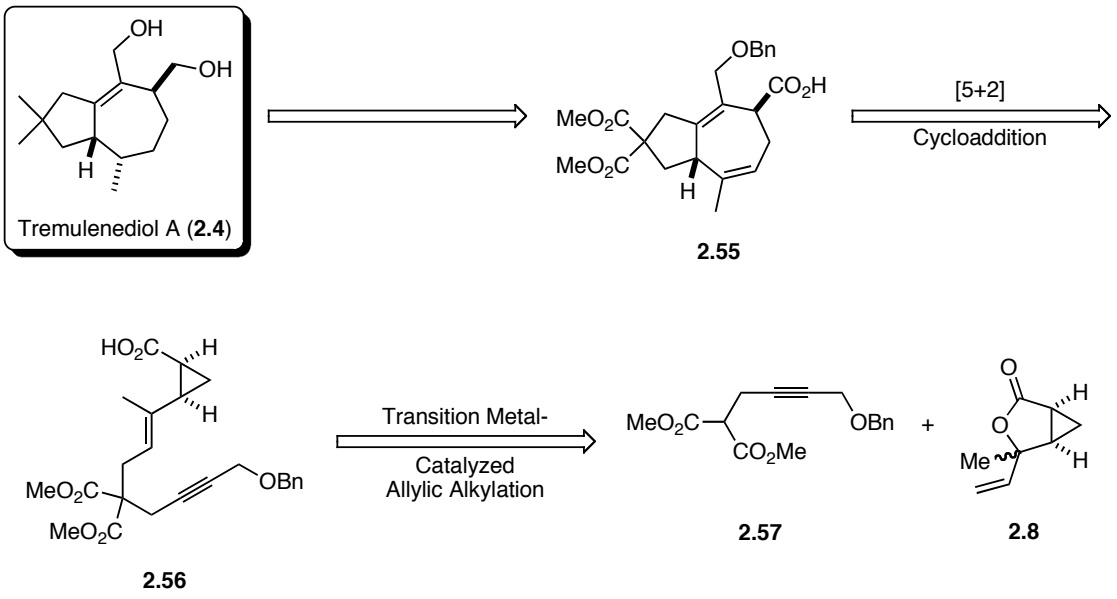
Although a number of difficulties had been encountered thus far in assembling the carbon framework present in **2.3** and **2.4**, we felt that the proposed rhodium(II)-catalyzed asymmetric cyclopropanation could still be used to set the stage for a diastereoselective intramolecular [5+2] cycloaddition as an efficient entry into the tremulane natural carbon skeleton. However, an alternate strategy for synthesizing the intermediate cyclopropyl enyne was necessary. Inspection of cyclopropyl lactone **2.8** revealed an allyl carboxylate moiety that could be exploited to access the desired 1,6-enyne *via* a transition metal-catalyzed allylic alkylation. The successful incorporation of this allylic substitution reaction in the synthetic approach would represent a third transition metal-catalyzed step in the synthesis.

Although the precedent established in the field allylic alkylations indicated that a palladium complex should be the most effective catalyst to provide the regioselectivity desired,[328] Evan's report of a modified Wilkinson's catalyst-mediated allylic alkylation captured our attention.[329] We reasoned that if $RhCl(PPh_3)_3/P(OMe)_3$ were capable of catalyzing the allylic alkylation of cyclopropyl lactone **2.8** with an appropriately functionalized alkyne regioselectively, the possibility of inducing the subsequent intramolecular [5+2] cycloaddition *in situ* was too attractive to ignore. If successful, a

novel rhodium(I)-catalyzed allylic alkylation/[5+2] cycloaddition sequence would represent a rapid entry into the [5.3.0] bicyclic core of tremulenediol A and tremulenolide A.

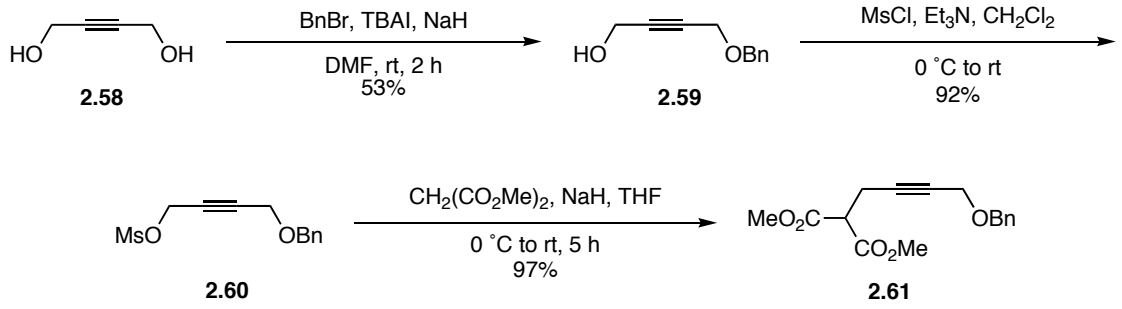
Although a tandem allylic alkylation/[5+2] cycloaddition sequence would provide an efficient and concise approach to the tremulanes, one unattractive aspect of this method would be the need to utilize the stabilized sodiodimethyl malonate derivative **2.57** in the rhodium(I)-catalyzed allylic alkylation. This requirement would then necessitate reduction of the *gem*-diester moiety in **2.55** to the *gem*-dimethyl functionality present in **2.3** and **2.4**. While this series of reduction steps would add to the number of synthetic operations, we felt that the rapid assembly of advanced intermediates utilizing a unique transition metal-mediated operation made this pathway worth exploring (Scheme 2.12).

Scheme 2.12



With our focus set squarely upon the exciting possibility of developing a novel rhodium(I)-catalyzed allylic alkylation/[5+2] cycloaddition process, our initial task was to synthesize the dimethyl malonate derivative **2.57** from commercially available 2-butyn-1,4-diol (**2.58**) in a straightforward three-step sequence (Scheme 2.13). Our first efforts to prepare alcohol **2.59** relied upon reports in which symmetrical diols such as **2.58** were selectively monobenzylated with Ag_2O and benzyl bromide.[330] Indeed, when diol **2.58** was treated with Ag_2O and BnBr, the monobenzylated product **2.59** was obtained, albeit in only 51% yield. Given the low yield and high cost of the silver-mediated monoalkylation reaction, we examined more conventional benzylation methods as less expensive alternatives. When diol **2.58** was treated with BnBr and NaH in THF, alcohol **2.59** was obtained in a mere 17% yield. By changing the solvent from THF to DMF only a slight increase in the yield (24%) was observed. Finally, during the course of optimizing this transformation, it was found that treatment of diol **2.58** with benzyl bromide, NaH, and tetrabutylammonium iodide (TBAI) in DMF, the desired monobenzylated product **2.59** could be obtained in 53% yield.[314] Although the yield was not significantly higher, this method represents a marked improvement over the use of costly silver oxide. Subsequent treatment of propargyl alcohol **2.59** with methanesulfonyl chloride (MsCl) and Et_3N in CH_2Cl_2 provided mesylate **2.60** in 92% yield.[331] It is noteworthy that extended reaction times for this transformation led to the formation of significant amounts of alkyl chloride *via* displacement of the labile propargylic mesylate. Treatment of mesylate **2.60** with sodiodimethyl malonate in THF gave **2.57** in 97% yield. With this optimized three-step sequence, multigram quantities of **2.57** could be obtained with an overall yield of 48% at relatively low cost.

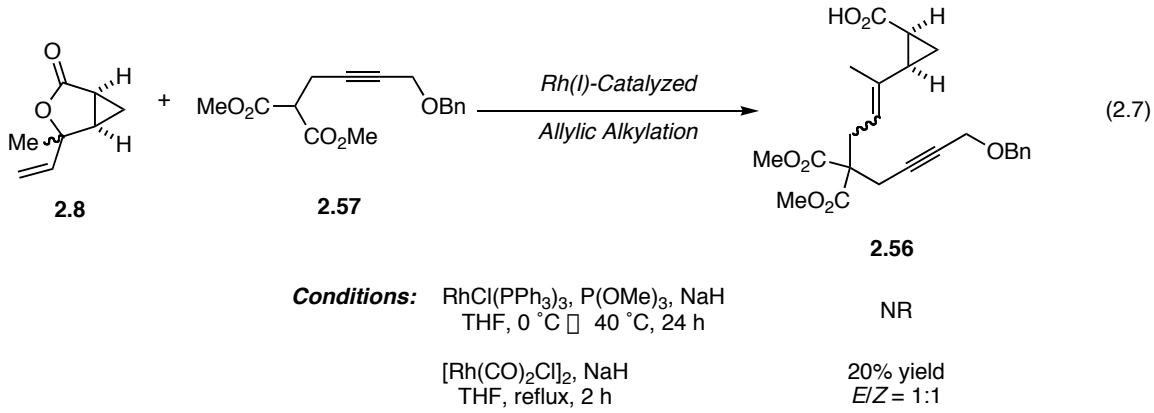
Scheme 2.13



With cyclopropyl lactone **2.8** and malonate **2.57** in hand, we turned our attention toward investigating the $RhCl(PPh_3)_3/P(OMe)_3$-catalyzed allylic alkylation. The main question that needed to be answered was whether the alkylation of cyclopropyl lactone **2.8** would provide the desired substitution product regioselectively. Would it follow the trend of palladium(0) catalysis and provide the desired product arising from alkylation at the less hindered allylic terminus, or would the regioselectivity mirror the results reported by Evan's to yield substitution products resulting from alkylation at the more substituted carbon? Although we were not optimistic that the regioselectivity would be in our favor, the potential development of a tandem [5+2] cycloaddition warranted examination.

When cyclopropyl lactone **2.8** was treated with the sodium enolate of malonate **2.57** in the presence of $RhCl(PPh_3)_3/P(OMe)_3$, allylic alkylation failed to proceed even after extended reaction times and elevated temperatures (Eq. 2.7). Repeated attempts with this catalyst system resulted in recovered starting material each time. We quickly learned that generating the active catalytic species in this reaction was not only experimentally sensitive but also difficult to reproduce. Even when simple, unsymmetrical allylic carbonates were used as test substrates, the reaction would often fail to provide the substitution product. However, if lactone **2.8** was treated with the anion of **2.57** in the presence of the dimeric rhodium(I) catalyst, $[Rh(CO)_2Cl]_2$, likewise

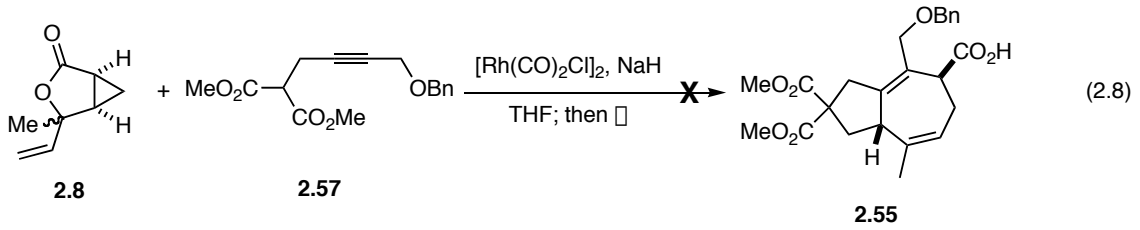
known for its ability to catalyze the desired intramolecular [5+2] cycloaddition, cyclopropyl enyne **2.56** was formed with complete regiocontrol as a mixture (1:1) of *E*/*Z* isomers. This regiochemical trend was quite surprising considering that Evans' results suggested that the opposite regioisomer should have been attained. Although the desired reaction took place, the transformation proceeded in a disappointing 20% yield. Attempts at optimizing the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation of **2.8** involved performing the reaction at lower temperatures (≥0 ˚C) for extended reaction times (2 to 48 h). However, these experiments failed to provide **2.56** in an improved yield.



(2.7)

Encouraged by the formation of cyclopropyl enyne **2.56** when lactone **2.8** was treated with malonate **2.57** in the presence of $[Rh(CO)_2Cl]_2$, focus shifted toward developing the tandem reaction sequence with the hope of isolating cycloadduct **2.55**. However, initial attempts to perform the one-pot, domino reaction under conditions similar to the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation failed to yield cycloadduct **2.55** (Eq. 2.8). Changing the solvent to PhMe led to problems associated with the solubility of the malonate anion, thereby leading to inefficient formation of enyne **2.56**. Attempts to circumvent this problem employing a mixed solvent system of toluene/THF (1:1) were also unsuccessful.

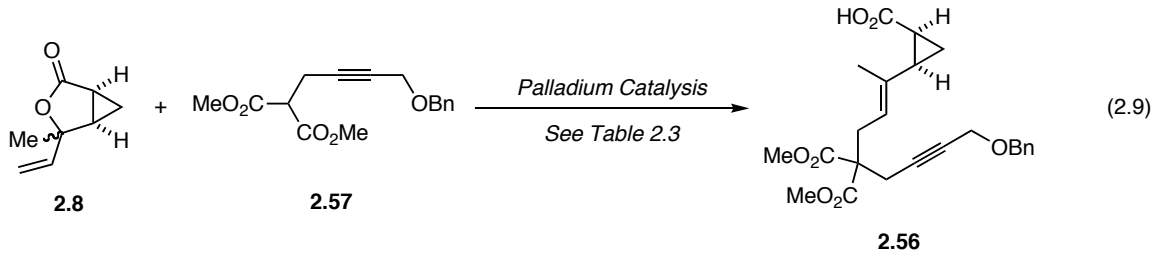
A number of factors may have contributed to the failure of the desired reaction. Some of these may include the ability of the rhodium catalyst to catalyze the [5+2] cycloaddition following the allylic alkylation, excess malonate present in the reaction mixture, or the coordinative aspects of the sodium carboxylate functionality. The absence of a carboxylic acid-substituted *cis*-cyclopropyl enyne undergoing the intramolecular [5+2] cycloaddition in Wender's studies may indicate that this functional group is not a viable substrate for this carbocyclization.[235] Subsequent studies on the cycloaddition of enyne **3.54**, which will be discussed shortly, suggest that this may be the case.



2.8 **2.57** **2.55** (2.8)

Given the poor efficiency with which $[Rh(CO)_2Cl]_2$ catalyzed the allylic alkylation of cyclopropyl lactone **2.8** with malonate **2.57**, we decided to examine other transition metals as alternative catalysts. We first focused on traditional palladium(0) catalysts that were known to provide substitution products with the regiochemistry we required (Eq. 2.9) (see Section 1.B.3.1). A summary of the conditions examined can be found in Table 2.3. We first examined the reaction of **2.8** with sodiomalonate **2.57** in the presence of $Pd(PPh_3)_4$.[312] This reaction afforded cyclopropyl enyne **2.56** in 49% yield after 4 hours at reflux (entry 1).[332] We speculated that diligent stoichiometric control of the base used to generate the enolate was required to ensure that formation of metal hydride complexes would not compete with generation of the (η^3-allyl)PdL_n complex.

Given the difficulties in controlling stoichiometry with NaH, a series of bases were screened that would allow for greater stoichiometric control. Thus, lithium diisopropylamine (LDA), lithium hexamethyldisilazide (LiHMDS), and potassium *t*-butoxide (*t*-BuOK) (entry 2) were all examined, but each failed to provide **2.56** in better yield.



2.8 **2.57** **2.56** (2.9)

The notorious instability of $Pd(PPh_3)_4$ may also have been to blame for incomplete conversion of cyclopropyl lactone **2.8** to enyne **2.56**.[332] Thus, other sources of palladium(0) were examined. Under "phosphine free" reaction conditions, $Pd_2(dba)_3$ and its recrystallized chloroform complex, $Pd_2(dba)_3 \bullet CHCl_3$, gave only 17% of the desired product (entries 3 and 4). The best single result that we observed was by generating the active allylic alkylation catalyst *in situ* from $Pd(OAc)_2$ and $P(O^iPr)_3$ while employing *n*-BuLi as the base (entry 5).[332] Under these conditions, cyclopropyl enyne **2.56** was obtained in 84% yield. Unfortunately, this result was not reproducible, and enyne **2.56** was often obtained in extremely low yields (<5%).

It is conceivable that some of the difficulties were associated with generating the active catalytic species. In early reports on palladium-catalyzed allylic alkylations, it was found that additional phosphine would sometimes improve the yield of otherwise troublesome reactions.[25] Therefore, use of $Pd_2(dba)_3 \bullet CHCl_3$ in the presence of an additional 70 mol% PPh_3 gave a substantially better yield of **2.56** (compare entries 4 and

6). However, when $Pd(dba)_2$ was employed under identical conditions cyclopropyl enyne **2.56** was obtained in a disappointing 15% yield (entry 7). On the other hand, treatment of cyclopropyl lactone **2.8** with the sodium enolate of **2.57** in the presence of 10 mol% $Pd(PPh_3)_4$ and 70 mol% PPh_3 gave enyne **2.56** in 74% yield (entry 8). This set of conditions proved very reliable even when the reaction was run on multigram scale. With an optimized set of conditions for the desired transformation in hand, our attention turned toward synthesizing the [5.3.0] bicycle *via* an intramolecular [5+2] cycloaddition.

Table 2.3. Palladium-catalyzed allylic alkylation of cyclopropyl lactone **2.8**[a]

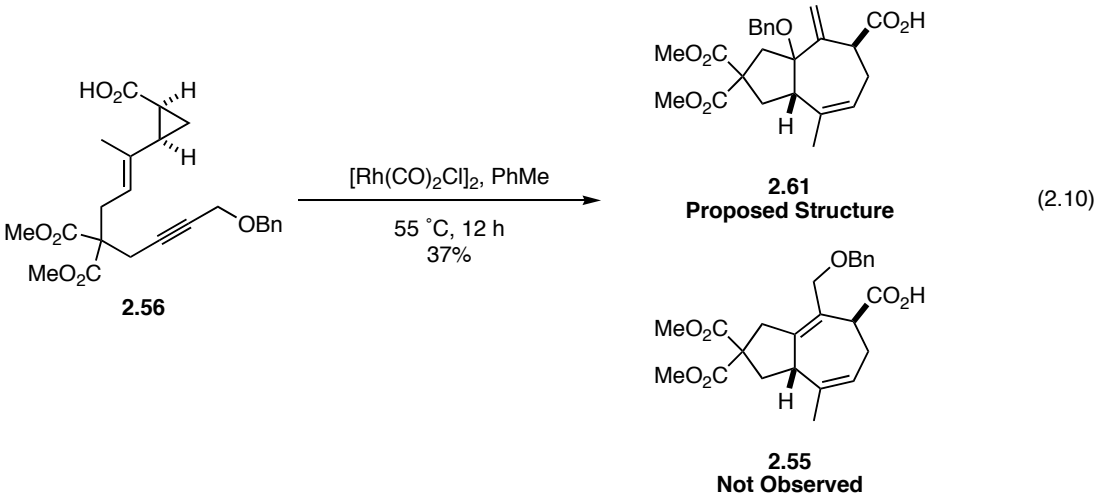
Entry	***Catalyst***	***Base***	***Yield(%)***[b]
1	$Pd(PPh_3)_4$	NaH	59
2	$Pd(PPh_3)_4$	^{t}BuOK	RSM
3	$Pd_2(dba)_3$	NaH	17
4	$Pd_2(dba)_3$•$CHCl_3$	NaH	17
5	***$Pd(OAc)_2$, $P(O^iPr)_3$***	***^{n}BuLi***	***84***[c]
6	$Pd_2(dba)_3$•$CHCl_3$, PPh_3	NaH	50
7	$Pd(dba)_2$, PPh_3	NaH	15
8	***$Pd(PPh_3)_4$, PPh_3***	***NaH***	***74***

[a]Conditions: 10 mol% Pd(0), 1.1 equiv of base, 1.2 equiv of **2.57**, 0.1M in THF with respect to **2.8**. [b]Isolated yields. [c]Result was irreproducible.

The absence of a *cis*-carboxylate substituted vinylcyclopropane, similar in structure to **2.56**, in Wender's 1999 study of regioselectivity in the [5+2] cycloaddition

may be because it was either not examined or failed to produce the [5+2] cycloadduct.[235] Hoping that the former and not the latter was the case, we went ahead and analyzed the intramolecular [5+2] cycloaddition of carboxylate **2.56** to assemble the tremulane carbon skeleton (Eq. 2.10).

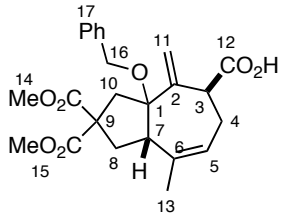
In an effort to induce the rhodium(I)-catalyzed [5+2] cycloaddition of cyclopropyl enyne **2.56** to furnish **2.55**, various combinations of catalyst, additive, solvent and temperature were examined (Table 2.4). The first rhodium(I) catalyst used was the dimeric complex $[Rh(CO)_2Cl]_2$ because of its greater propensity to yield cycloadducts resulting from cleavage of the more substituted cyclopropane bond. Thus, when a solution of **2.56** containing $[Rh(CO)_2Cl]_2$ in toluene was heated to 55 ˚C, an unknown by-product was obtained in 37% yield after 12 h. After careful examination of the ^1H and ^{13}C NMR spectra, additional ^1H-^1H NMR correlation (COSY) and ^1H-^{13}C NMR correlation (HMQC) experiments, and mass spectral analysis the allylically transposed benzyl ether **2.61** was most consistent with the spectral data.



(2.10)

Mass spectral analysis of **2.61** provided an M+1 peak of 429 consistent with both the proposed structure and cycloadduct **2.55**. However, the NMR data was more conclusive, and the resonances that led us to the proposed structure **2.61** are listed in Table 2.3. The multiplet at 5.30-5.27 coincides with the olefinic proton on C5 that had a ^{13}C shift of 120.6 ppm. The HMQC experiment indicated that the protons whose chemical shifts corresponded to 5.18 and 5.12 resided on the same carbon with a resonance of 108.7 ppm. This data suggests that these signals derive from a terminal olefinic methylene consistent with C11 on **2.61**. The benzyl protons on C16 gave a rather unusual signal. Instead of the expected two signals integrating to one proton each with a large geminal coupling constant, we observed one singlet that integrated to two protons. This was not the first time we witnessed this phenomena and it will be discussed later in the synthesis of other cycloadducts. The rest of the resonances associated with the carbocyclic ring protons listed in Table 2.3 are consistent with the proposed structure of **2.61**. The regioselectivity of the [5+2] cycloaddition was determined by examination of the long range ^{1}H-^{13}C NMR correlation (HMBC) experiment. These results showed a strong correlation between the ^{1}H NMR olefinic signals on C11 and the ^{13}C NMR resonances of C3 and C1 as well as the C3 proton and the carboxylate carbonyl carbon.

Table 2.3. Principle NMR spectral data for cycloadduct **2.61**.



2.61

Assignment[a]	*^{1}H NMR δ*[b]	*Multiplicity*	*Coupling Constant J*[c]	*^{13}C NMR δ*[b]
C5-1H	5.30-5.27	m	–	120.6
C11-1H[d]	5.18	app t	1.0	108.7
C11-1H[d]	5.12	app t	1.0	108.7
C16-2H	4.71	s	–	65.4
C3-H	3.27-3.25	m	–	45.7
C10-1H[d]	3.04	d	15.5	40.9
C7-1H	2.95-2.91	m	–	54.1
C10-1H[d]	2.92	d	15.5	40.9
C8-1H[d]	2.78	ddd	14.0, 6.0, 1.0	35.9
C4-1H[d]	2.76-2.71	m	–	34.5
C4-1H[d]	2.55-2.49	m	–	34.5
C8-1H[d]	1.89	dd	14.0, 13.0	40.9

[a]Indicates the carbon and number of hydrogens associated with the resonance. [b]Measured in ppm.
[c]Measured in Hz. [d]*Geminal* coupling indicated by HMQC experiment.

At this point, we felt that by synthesizing a crystalline derivative of **2.61** suitable for X-ray analysis we could determine whether or not the proposed structure was correct. To achieve this, we envisioned that reduction of the corresponding carboxylic acid moiety to the primary alcohol and subsequent acylation with either a *p*-bromo- or *p*-nitrobenzoyl chloride should yield suitable a solid suitable for X-ray crystallography. Surprisingly, the carboxylic acid moiety in **2.61** proved resistant to reduction to the corresponding alcohol (Table 2.4). Attempted reduction under standard conditions with borane reagents[333,334] only returned starting material from the mixture, even after prolonged reactions times (>48 h) (entries 1 and 2). Lewis acid mediated reduction of **2.61** with BF_3•OEt_2 and $NaBH_4$ gave a complex mixture of products (entry 3). Attempts at reducing **2.61** through the *in situ* generation of the mixed anhydride again failed (entries 4 and 5). Compound **2.61** was also treated with $LiAlH_4$ and $LiBHEt_3$, but a complex mixture of products was obtained from which the desired triol could not be isolated.

Table 2.4. Attempted carboxylic acid reduction of compound **2.61**.

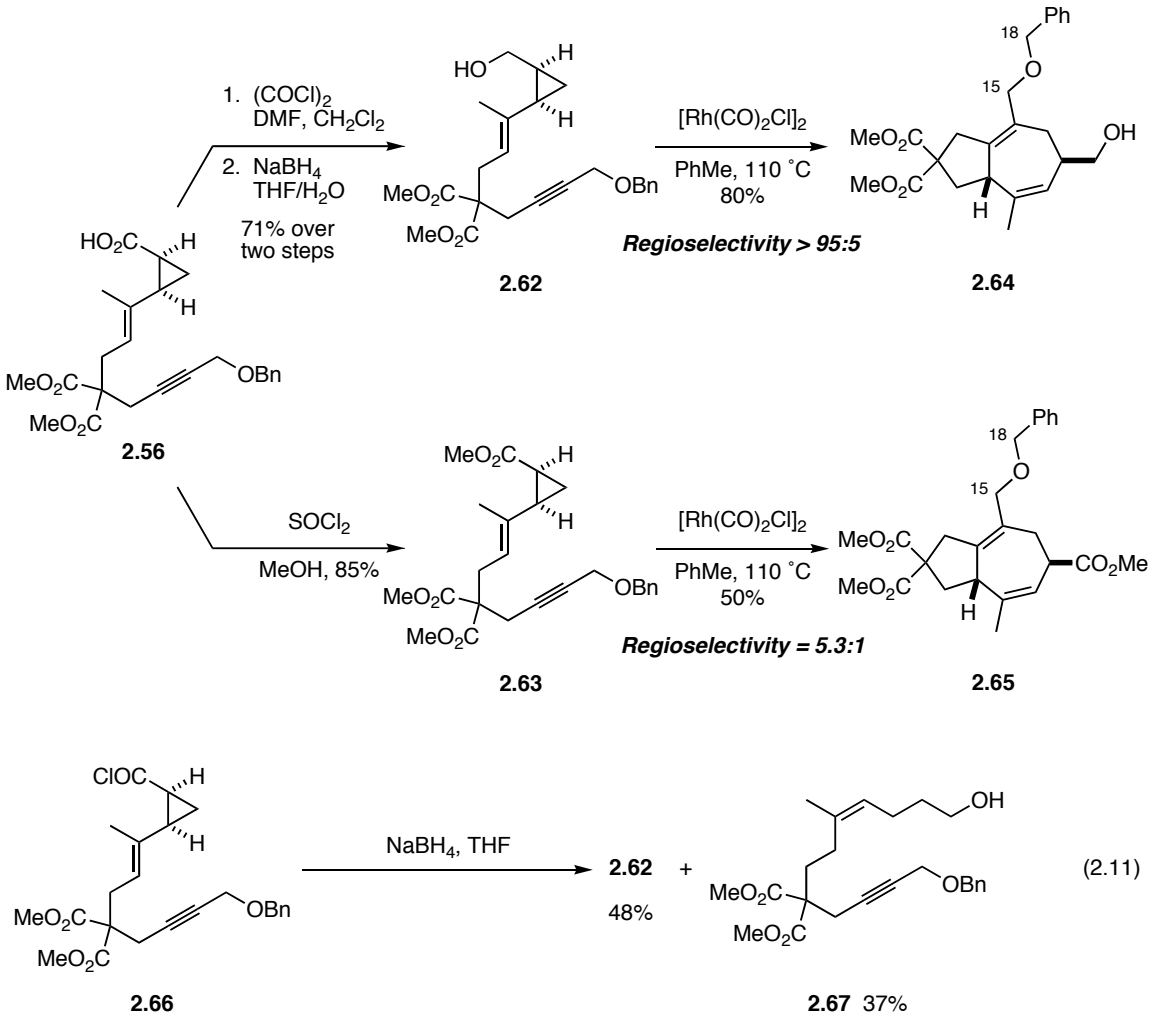
Entry	*Conditions*	*Result*
1	BH_3•THF	Recovered Starting Material
2	BH_3•DMS	Recovered Starting Material
3	BF_3•OEt_2, $NaBH_4$	Complex Mixture of Products
4	$ClCO_2Me$, Et_3N, then $NaBH_4$, MeOH	Recovered Starting Material
5	$ClCO_2{}^iBu$, NMM, DME, then $NaBH_4$, MeOH	Recovered Starting Material
6	$LiAlH_4$	Complex Mixture of Products
7	$LiBHEt_3$	Complex Mixture of Products

In order to gain some insight into the structural nature of compound **2.61**, a series of analogous cyclopropyl enynes were synthesized in which the nature of the *cis* functional group on the cyclopropane was varied. It was thought that [5+2] cycloaddition of these substrates should yield spectroscopic data that may lead to useful insights into the structure of **2.61**. A survey of the literature prompted us to prepare the two cyclopropyl enynes **2.62** and **2.63** whose corresponding [5+2] cycloadducts could be easily compared to published spectral data (Scheme 2.14). Cyclopropyl enyne **2.62** was obtained by treatment of carboxylic acid **2.56** with oxalyl chloride and DMF to give an intermediate acid chloride that was then reduced with $NaBH_4$ to provided **2.62** in 71% yield over the two steps.[335] Interestingly, when the $NaBH_4$ reduction of **2.66** was

performed under anhydrous conditions, the alcohol **2.67**, resulting from 1,6-hydride addition into the vinyl cyclopropane moiety could be isolated in 37% yield (Eq. 2.11). In an attempt to circumvent the formation of **2.67**, Luche reduction conditions were explored.[336] Unfortunately, this reaction proved problematic due to the insolubility of $CeCl_3 \bullet 7H_2O$ in THF. It was eventually discovered that when the reduction was conducted in the presence of water (~10 vol%) at 0 ˚C, the alcohol **2.62** could be obtained in good yield. Treatment of cyclopropyl enyne **2.56** with thionyl chloride in methanol gave the triester **2.63** in 85% yield.

Subsequent [5+2] cycloaddition of **2.62** and **2.63** with $[Rh(CO)_2Cl]_2$ at 110 ˚C provided cycloadducts **2.64** and **2.65** in 80% and 50% yield, respectively. Both alcohol **2.62** and ester **2.63** provided cycloadducts resulting from cleavage of the less substituted cyclopropane bond. The regiochemistry in the [5+2] cycloaddition of **2.62** and **2.63** was determined by HMQC and HMBC NMR experiments as well as comparison of spectral data to Wender's results. When comparing the ^{1}H NMR spectra of cycloadducts **2.64** and **2.65** to the spectral data associated with compound **2.61** a number of significant differences were apparent. Alcohol **2.64** displayed doublets (J = 11.5 Hz) at 4.06 and 4.03 ppm for the geminal C15 protons. However, the benzyl methylene C18 protons produced a singlet at 4.45 ppm that integrated to two protons similar to what was observed with compound **2.61**. Interestingly, the ^{1}H NMR of ester **2.65** showed a complex signal at 4.45 ppm for the two benzylic C18 protons, and a broad singlet at 4.04 ppm assigned to the allylic C15 protons. These results seem to suggest that the signal which corresponds to the benzylic protons on cycloadduct **2.61** can at times appear as a singlet around 4.50 ppm that integrates to two protons on [5.3.0] bicyclic compounds.

Scheme 2.14



Our first thought was to determine whether the formation of **2.61** could be suppressed by changing the reaction conditions used for the [5+2] cycloaddition. If the reaction was performed at 110 ˚C for 2 h, compound **2.61** was obtained in 57% yield (entry 1). Switching catalytic systems to the modified Wilkinson's catalyst ($RhCl(PPh_3)_3$/AgOTf) as reported by Wender led to no improvement, and provided **2.61** in 25% yield (entry 2). A series of solvents were examined for their compatibility in the [5+2] cycloaddition. It has been reported that the use 1,2-dichloroethane (DCE) effects

clean conversion of cyclopropyl enynes to their corresponding [5+2] cycloadducts.[337] Unfortunately, performing the cycloaddition in DCE at 90 ˚C and 110 ˚C only gave **2.61** in 57% and 49% yield, respectively (entries 3 and 4). THF was also examined, but either the starting enyne **2.56** was recovered or, after extended reaction times at elevated temperatures, baseline material was observed by TLC (entry 5).

Table 2.5. Conditions explored in the attempted [5+2] cycloaddition of enyne **2.56**.[a]

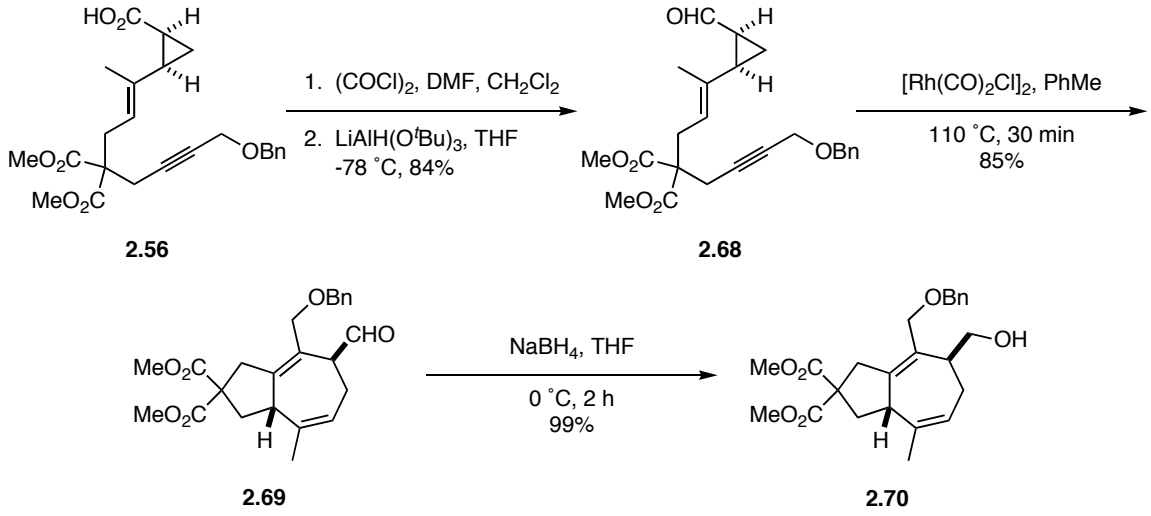
Entry	*Catalyst*	*Solvent*	*Temperature (˚C)*[b]	*Yield(%) of 2.61*[c]
1	$[Rh(CO)_2Cl]_2$	PhMe	110	57%
2	$RhCl(PPh_3)_3$/AgOTf	PhMe	110	25%
3	$[Rh(CO)_2Cl]_2$	DCE	90	57%
4	$[Rh(CO)_2Cl]_2$	DCE	110	49%
5[d]	$[Rh(CO)_2Cl]_2$	THF	110	NR

[a]Conditions: 10 mol% of Rh(I), 0.01M in dry, degassed solvent relative to **2.56**. [b]Bath temperatures. [c]Isolated yields. [d]Reaction run in a sealed screw-cap vial.

At this juncture, we reexamined Wender's results and observed that the regioselective cleavage of the more substituted cyclopropane bond of *cis*-cyclopropyl enynes occurred when a formyl-substituted *cis*-cyclopropyl enyne was heated in the presence of $[Rh(CO)_2Cl]_2$ in PhMe. Therefore, acid **2.56** was converted to the corresponding aldehyde **2.68** in a straightforward sequence of transformations (Scheme 2.15). Thus, treatment of carboxylic acid **2.56** with oxalyl chloride and DMF followed by reduction of the crude acid chloride with $LiAlH(O^tBu)_3$ provided aldehyde **2.68** in 84% yield.[338] The alcohol **2.62** was also obtained as a side product in 12% yield, but it

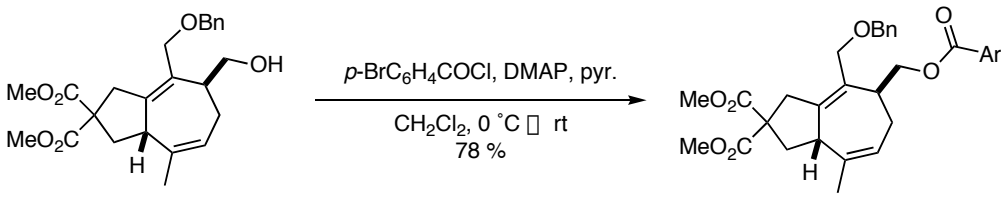
was oxidized quantitatively with Dess-Martin periodinane to bring the overall yield of this sequence to 96%.[339] Heating of **2.68** in the presence of $[Rh(CO)_2Cl]_2$ provided the desired cycloadduct **2.69** in 85% yield with complete regioselectivity. The regiochemistry in the cycloaddition of **2.68** was apparent by analysis of the HMQC and HMBC NMR data in addition to comparisons made to Wender's reported spectral data. Subsequent reduction of aldehyde **2.69** with $NaBH_4$ gave the primary alcohol **2.70** in 83% yield.

Scheme 2.15



With alcohol **2.70** in hand, efforts were focused on obtaining a crystal of a suitable derivative that would provide further structural verification. Acylation of **2.70** with *p*-bromobenzoyl chloride in the presence of DMAP yielded benzoate **2.71** in 78% yield as an amorphous solid (Eq. 2.12).[340] Unfortunately, all attempts to recrystallize **2.71** to provide a crystalline solid suitable for X-ray analysis failed. A number of other derivatives were also synthesized, but the tremulane core proved resistant to all crystallization efforts. Therefore, the most straightforward method to confirm the

structural assignments would be to complete the synthesis and compare synthetic and natural spectroscopic data for tremulenediol A.



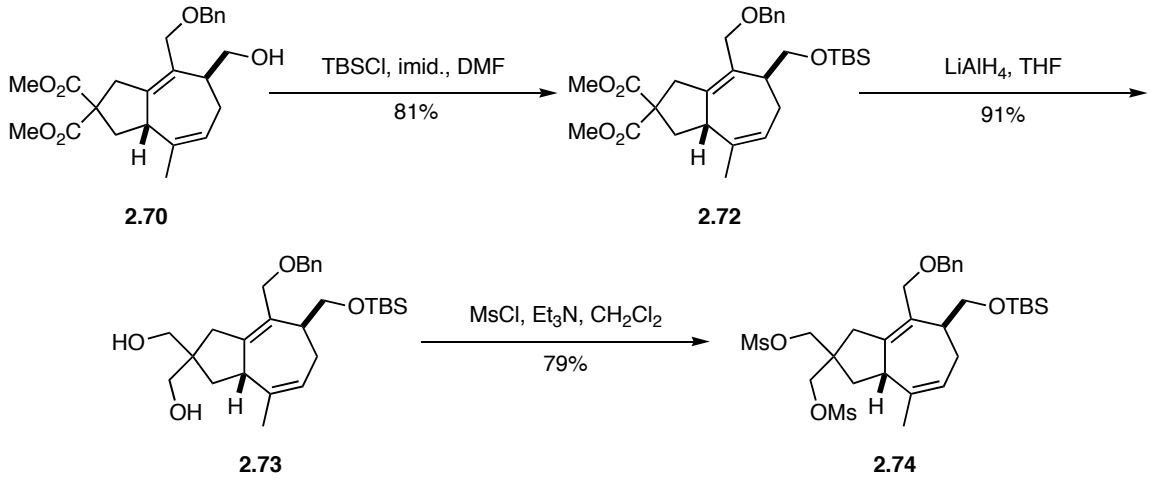
(2.12)

2.70

2.71: Ar = *p*-BrC_6H_4

To this end, our efforts focused on the task of completely reducing the diester moiety to install the requisite *gem*-dimethyl substitution present in tremulanes **2.3** and **2.4**. Our initial protecting group strategy was to treat alcohol **2.70** with benzyl bromide and NaH in the presence of TBAI to allow for concomitant removal of both alcohol protecting groups in one operation. Unfortunately, attempts at incorporating an additional benzyl ether moiety under the conditions described failed to yield the dibenzylated product. Acid-catalyzed benzylation utilizing the trichlorobenzyl imidate in the presence of TMSOTf also proved futile. Thus, alcohol **2.70** was protected as its TBS-ether by treatment with TBSCl and imidazole to provide **2.72** in 81% yield (Scheme 2.16).[341] Surprisingly, when diester **2.72** was treated with DIBALH in PhMe, not only did reduction of the methyl esters occur to provide the 1,3-diol moiety, but silyl deprotection also took place. Removal of TBS-ethers using DIBALH has been reported in the literature, but in all those cases, CH_2Cl_2 was used as the solvent.[342] Gratifyingly, reduction of **2.72** with $LiAlH_4$ gave 1,3-diol **2.73** in 91% yield.[343] Subsequent treatment of diol **2.73** with methansulfonyl chloride (MsCl) and Et_3N provided bismesylate **2.74** in 79% yield.[344]

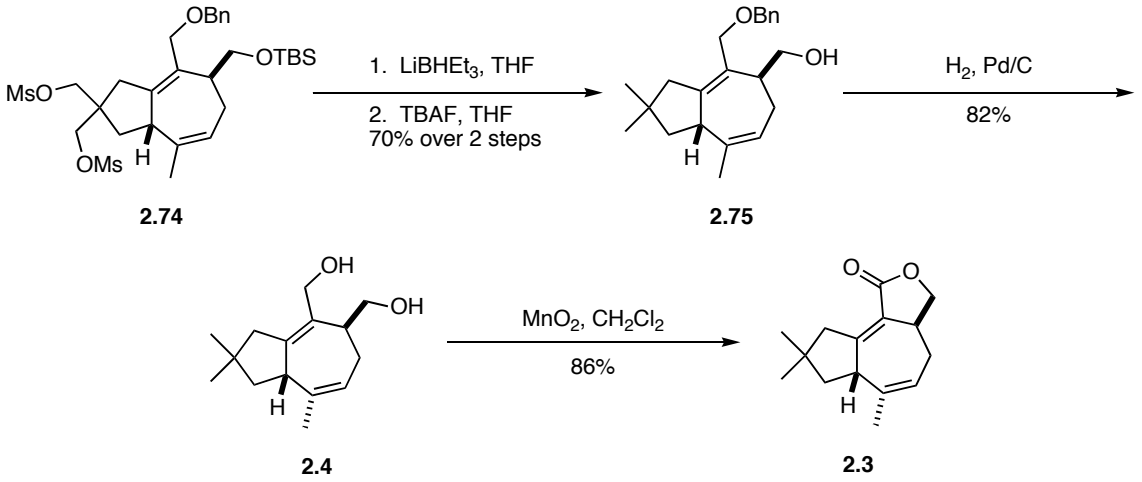
Scheme 2.16



Initial attempts to reduce the bismesylate functionality in **2.74** to provide the *gem*-dimethyl moiety were performed utilizing $LiAlH_4$. However, the reaction never proceeded to completion, and a monomesylate intermediate was recovered, even after extended reaction times (>24 h). Ultimately, the reduction of **2.74** was accomplished using $LiBHEt_3$ as the reductant to provide the *gem*-dimethyl intermediate. Subsequent treatment with TBAF in THF induced removal of the TBS protecting group to give **2.75** in 70% yield over the two steps (Scheme 2.17). With the *gem*-dimethyl intermediate **2.75** in hand, heterogeneous catalytic hydrogenation with base-washed palladium on carbon under an atmosphere of H_2 chemoselectively reduced the trisubstituted olefin with concomitant removal of the benzyl protecting group to provide tremulenediol A in 82% yield. This reduction occurred diastereoselectively to establish the third and final stereocenter on the tremulane carbon skeleton by delivering hydrogen from the less sterically hindered convex face of the [5.3.0] bicyclic core. The spectral data for **2.4** was identical in all respects to that reported in the literature. The absolute configuration of **2.4** was determined by comparison of the optical rotation ($[\square]_D^{24} = 40.0^\circ$ (*c* 0.24 MeOH))

to that for the isolated natural product ($[\square]_D^{24}$ = 41.3° (*c* 0.24 MeOH)) Subsequent treatment of **2.4** with MnO_2 provided lactone **2.3**.

Scheme 2.17



2.5 CONCLUSIONS

In summary, a concise synthesis of two representative sesquiterpene metabolites of the class *tremulane* has been achieved. The synthetic route is highlighted by a chiral rhodium(II)-catalyzed enantioselective cyclopropanation to establish the absolute stereochemistry necessary in the two target tremulanes, tremulenediol A and tremulenolide A. A transition metal-catalyzed allylic alkylation is then utilized to assemble the complete carbon ensemble present in the natural products, as well as set up a diastereoselective rhodium(I)-catalyzed [5+2] intramolecular cycloaddition. These studies led to the discovery and development of a novel $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation reaction with unusual regioselectivity. Additionally, this method has since been expanded to include domino $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation/carbocylization reactions as ways in which to gain access to complex cyclic

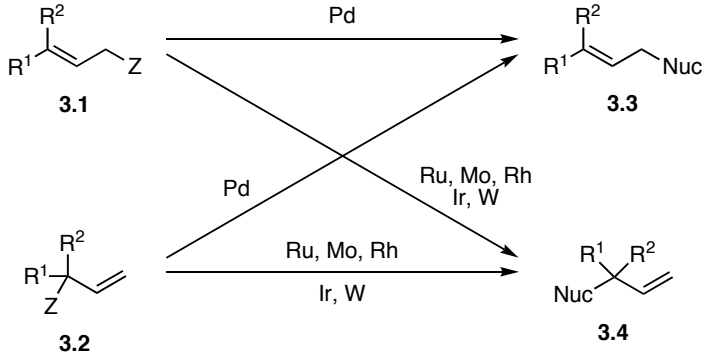
carboskeletal frameworks. The trio of transition metal-catalyzed operations described herein represents a convergent and highly efficient enantioselective entry into the tremulane carbon skeleton. A series of relatively straightforward synthetic manipulations completes the total synthesis of **2.3** and **2.4**. Tremulenediol A was obtained in 16 steps and in an 8% overall yield. Although the total number of steps is comparable to Davies' synthesis, the overall yield of our approach is better by 10-fold.

Chapter 3. $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylations

3.1 INTRODUCTION

Transition metal-catalyzed allylic alkylations constitute one of the more widely utilized classes of reactions in modern synthetic organic chemistry.[2,5,12,25,33,345-348] Recent efforts in this area have focused on the development of catalysts that enable high regio- and stereochemical control in substitution reactions involving symmetrical and unsymmetrical allylic substrates. Palladium-catalyzed processes typically favor nucleophilic substitution at the sterically less hindered allylic terminus, irrespective of the structure of the starting materials (*e.g.*, **3.1** or **3.2**), to yield substitution products **3.3**.[8] However, Ru,[104,349,350] Mo,[116] Rh,[105,107,120,329] Ir[91] and W[98] preferentially deliver products **3.4** that arise from substitution at the more substituted allylic terminus (Scheme 3.1).[2,25,33,101,106,345-348] The reader is referred to section 1 of chapter 1 in which the regio- and stereochemical trends associated with each metal catalyst is discussed. These reactions are generally believed to proceed *via* transition metal-stabilized allyl intermediates that may range in structure from an unsymmetrical π^1-complex to a symmetrical π^3-allyl complex. The regioselectivity of the ensuing nucleophilic attack is dictated by a combination of steric and electronic factors that vary with the intermediate complex and the nucleophile.[19]

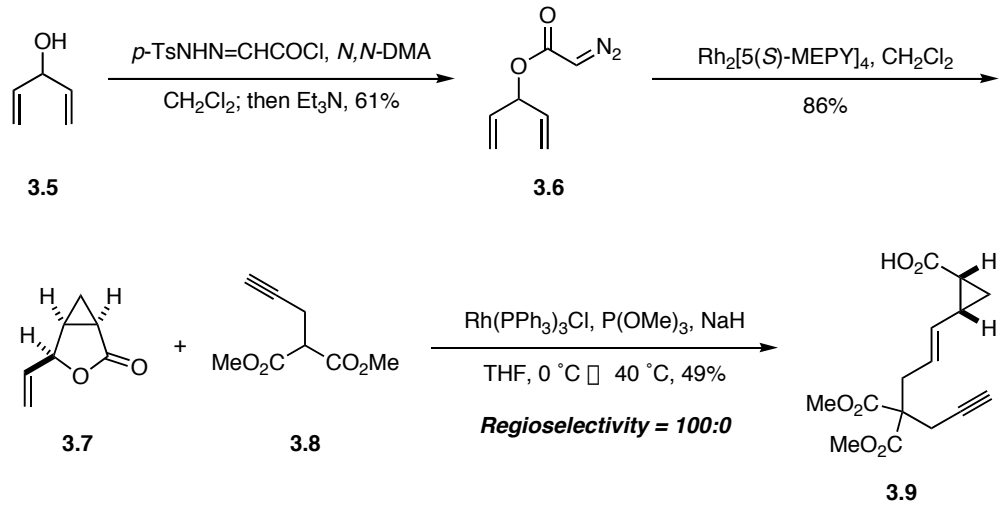
Scheme 3.1



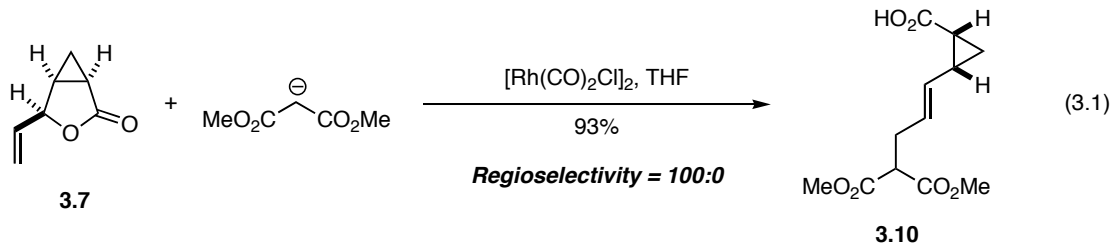
During our investigations into a domino rhodium(I)-catalyzed allylic alkylation/[5+2] cycloaddition to assemble rapidly the [5.3.0] bicyclic core of tremulenediol A and tremulenolide A, we initially examined how $RhCl(PPh_3)_3/P(OMe)_3$ would catalyze the allylic alkylation of cyclopropyl lactone **3.7** with sodiomalonate **3.8** (Scheme 3.2). We hoped that given the literature precedent for the Wilkinson's catalyst mediated [5+2] cycloaddition, the allylic alkylation catalyzed *via* Evan's protocol would lend itself to an efficient domino process. Lactone **3.7** was synthesized in two steps from commercially available divinyl carbinol **3.5**. Diazoesterification of alcohol **3.5** following the Corey-Myers procedure[311] provided diazoester **3.6** in moderate yield. Asymmetric cyclopropanation of diazoester **3.6** with the dirhodium(II) catalyst $Rh_2[5(S)\text{-MEPY}]_4$ provided the known cyclopropyl lactone **3.7** as one diastereomers in good yield (86%).[191] When cyclopropyl lactone **3.7** was treated with the sodium salt of malonate **3.8** in the presence of $RhCl(PPh_3)_3/P(OMe)_3$, the expected substitution product resulting from alkylation at the more substituted site was not observed. However, the ring-opened product **3.9**, resulting from nucleophilic attack at the terminal olefinic site, was obtained in 49% yield as the sole regioisomer. In addition to the low yield obtained from this transformation, we encountered significant difficulties associated with generating the

active catalyst species *in situ* through the described incubation procedure. All too often the reaction was not initiated, leading to recovered starting material.

Scheme 3.1



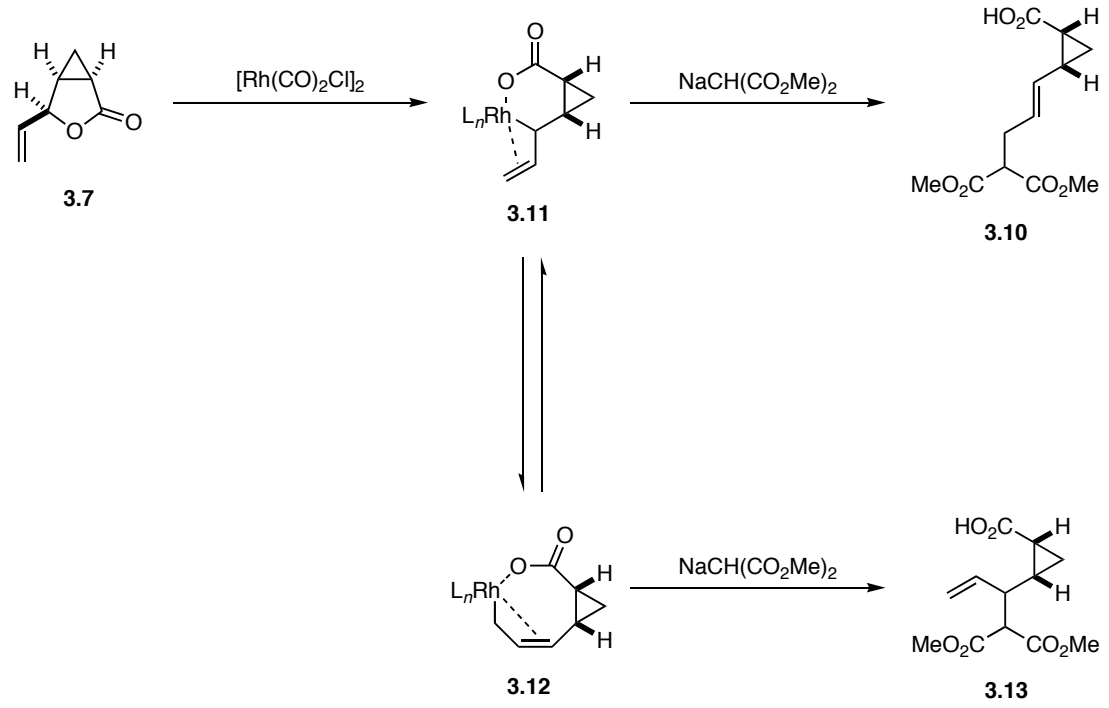
Given the difficulties associated with generating the active catalyst species and low yield in going from cyclopropyl lactone **3.7** to enyne **3.9**, we pondered whether $[Rh(CO)_2Cl]_2$ dimeric rhodium(I) catalyst, also known for its ability to catalyst the [5+2] cycloaddition, would promote the allylic alkylation of **3.7**. Thus, when cyclopropyl lactone **3.7** was treated with sodiodimethyl malonate in the presence of $[Rh(CO)_2Cl]_2$, carboxylic acid **3.10** was obtained in 93% yield and with complete regiocontrol (Eq. 3.1). The mode of regioselection observed in these $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations of **3.7** to give **3.9** is that which would be expected by palladium. According to Evans, rhodium(I)-catalyzed allylic alkylations should yield the opposite regioisomer. Therefore, we examined whether $[Rh(CO)_2Cl]_2$ was indeed an efficient allylic alkylation catalyst with regiochemical trends similar to palladium catalysts, or if cyclopropyl lactone was merely an anomalous case.



(3.1)

The regioselectivity of these rhodium-catalyzed alkylations of cyclopropyl lactone **3.7** was intriguing, and we were curious as to its origin. One reason for the reversal of regioselectivity maybe be attributed to detrimental steric interactions that would result from nucleophilic addition at the more substituted allylic carbon. Although sterics may play a part in directing the alkylation, the substitution of tertiary allylic carbonates at the more substituted carbon with the modified Wilkinson's catalyst as reported by Evan's makes this unlikely to be the determining factor. Because **3.7** is a vinyl lactone, the allylic leaving group cannot disassociate itself from the incipient π-allyl metal complex upon oxidative addition of the transition metal catalyst, the carboxylate is then allowed to interact with the cationic metal complex. The position of the carboxylate moiety within the rhodium(III)-bound intermediate may influence the regiochemical outcome of the reaction through the formation of a chelated intermediate as depicted in Scheme 3.2. Initial oxidative addition of the rhodium(I) complex to the vinyl cyclopropyl lactone **3.7** provides an allylmetal intermediate to which the carboxylate moiety could then coordinate. Thus, an equilibrium mixture of a six (**3.11)** and an eight (**3.12**)-membered chelate results. Upon alkylation of the presumably more stable six-membered chelate **3.11** would provide the formal direct substitution product **3.10**, whereas alkylation of the eight-membered chelate **3.12** would result in the unobserved malonate **3.13**.

Scheme 3.2



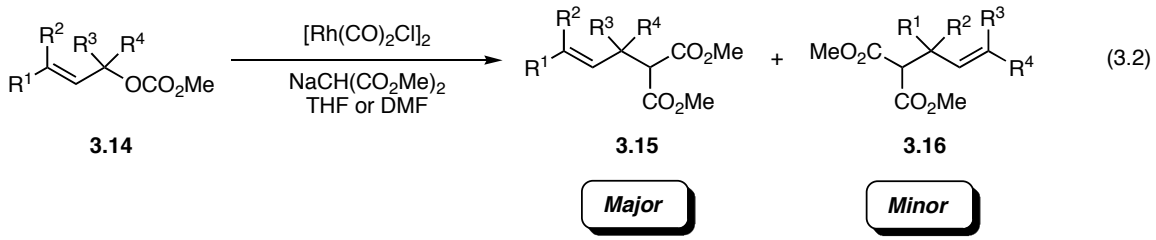
3.7 3.11 3.10 3.12 3.13

Given the unusual regioselectivity observed in the $[Rh(CO)_2Cl]_2$-catalyzed alkylation of lactone **3.7** with malonate nucleophiles, we decided to explore further this reaction to determine whether the regioselectivity was more general. We thus discovered a transition metal-catalyzed allylic alkylation that proceeded with unprecedented regiocontrol. It is generally possible to prepare either **3.3** or **3.4** through a judicious selection of catalyst and allylic substrate **3.1** or **3.2**, given the various catalysts capable of promoting allylic alkylations. However, a direct correlation between the structure of **3.1** or **3.2** and the major product may not exist, a situation that might be a disadvantage in certain instances. Indeed, in all the reports of allylic alkylations, no *single* catalyst has yet been identified that allows for direct, stereoselective allylic substitution at the carbon atom bearing the leaving group. Moreover, if such a catalyst were discovered that was also capable of promoting subsequent transformations, the potential to develop a variety

of cascade sequences exists. When the efficacy of $[Rh(CO)_2Cl]_2$ was examined in more detail as an allylic alkylation catalyst, and a series of carbocyclization reactions, we realized that this dimeric rhodium(I) species provided an opportunity to address these issues.

3.2 $[Rh(CO)_2Cl]_2$-CATALYZED DIRECT SUBSTITUTION OF SIMPLE UNSYMMETRICAL CARBONATES WITH DIMETHYL MALONATE

The observation that $[Rh(CO)_2Cl]_2$ catalyzed the rapid and highly regioselective allylic alkylation of carbonate **3.14a** (R^1 = Et, R^2–R^4 = H) with sodiodimethyl malonate to provide **3.15a** (R^1 = Et, R^2–R^4 = H) immediately captured our attention because the regiochemical outcome was opposite to that observed by Evans for allylic alkylations catalyzed by $RhCl(PPh_3)_3/P(OMe)_3$ (Eq. 3.2).[106] We therefore explored the scope of this novel $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation, and some of our preliminary findings are summarized in this section.

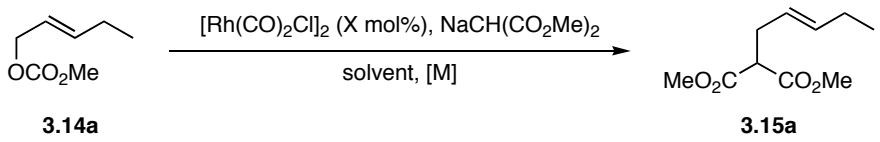


(3.2)

3.2.1 Optimizing Condition for the $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation

In an effort to determine the optimal conditions for this novel allylic alkylation, we examined a few core reaction parameters. Our focus was initially limited to varying the nature of the solvent, the concentration of reactants and the catalyst loading to evaluate changes in efficiency. We quickly determined that the reaction temperature, and

to a lesser extent the solvent, exhibited a marked effect on the regiochemistry of the reaction. Allylic carbonate **3.14a** was chosen as the first test substrate due to its reactivity in the alkylation reaction (Eq. 3.3).



3.14a **3.15a** (3.3)

We first examined solvent effects using five common solvents, as the medium for the reaction of **3.14a** with the sodium anion of dimethyl malonate to provide **3.15a** (Table 3.1). The reaction proceeded efficiently in most solvents (entries 1-4), although the reaction was particularly sluggish when run in toluene (entry 5), providing a mere 51% yield of the desired substitution product. These problems may have arisen from the low solubility of sodiodimethyl malonate in toluene. Albeit excellent yields of **3.15a** were obtained with MeCN and Et_2O respectively, the reactions were sluggish in these solvents, taking upwards of 10-12 hours to reach completion. Again, the malonate anion was only partially soluble in these solvents.

Table 3.1. Solvent effects on the $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Substitution Reaction of Carbonate **3.14a** with Sodiodimethyl Malonate[a]

Entry	*Solvent*	*Yield (%)*
1	DMF	91
2	THF	84
3	MeCN	95
4[b]	Et_2O	90
5[b]	PhMe	51

[a]Conditions: 5 mol% of $[Rh(CO)_2Cl]_2$, 2.5 equiv. of $CH_2(CO_2Me)_2$, 2.0 equiv. of NaH, 0.1M in carbonate **3.14**, room temperature, 2-4 h. **3.15a/3.16a** = 97:3. [b]Reaction run for 24 h.

We next examined how the rate of the reaction varied by altering the catalyst load. A low catalyst loading would be ideal to reduce the amount of catalyst and the overall cost of performing the transformation. The results of these studies are summarized in Table 3.2. Essentially, 5 mol% of $[Rh(CO)_2Cl]_2$ can be used to catalyze the alkylation efficiently (entry 2), but the reaction rate decreased to 4 h in comparison to 1 h with 10 mol% of catalyst. When 1 mol% of the catalyst was employed, the rate of the reaction plummeted, providing only 16% of malonate **3.15a**, even after allowing the reaction to proceed for over 24 h.

Table 3.2. Effect of Catalyst Loading on the $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Substitution Reaction of Carbonate **3.14a** with Sodiodimethyl Malonate[a]

Entry	*Catalyst Load*	*Yield (%)*
1[b]	1 mol%	16
2	5 mol%	85
3	10 mol%	84

[a]Conditions: 2.5 equiv. of $CH_2(CO_2Me)_2$, 2.0 equiv. of NaH, 0.1M in THF, room temperature, 2-4 h. **3.15a/3.16a** = 97:3. [b]Reaction run for 24 h.

The concentration of reactants in transition metal-catalyzed transformations plays an important role in determining the efficiency and rate of the reaction, particularly when utilizing a low catalyst load. If the concentration is too low, the rate of catalyst turnover proves to be too slow to effect the desired reaction in a reasonable amount of time. However, if the concentration is too high, issues of insolubility or competing reaction pathways (*i.e.* readdition of the leaving group to the π-ally intermediate thereby producing mixtures of allylic carbonates) become detrimental factors. To establish the optimal concentration in which the $[Rh(CO)_2Cl]_2$-catalyzed allylic substitution could be run, a series of reactions were run in which the concentration with respect to carbonate **3.14a** was varied, and the results are tabulated below in Table 3.3. The best yields of alkylation product **3.15a** were obtained when the reaction was run at a concentration of 0.1 M (entry 2). However, when the concentration of **3.14a** was increased to 0.5 M, the yield of the reaction plummeted to <10% as insolubility issues complicated the transfer of reagents, in particular the sodium salt of dimethyl malonate (Entry 3). Under high dilution conditions (0.01 M with respect to **3.14a**) the reaction proved less efficient, providing malonate **3.15a** in only 68% yield after an inordinate reaction time (>24 h)

(entry 1). Therefore, the standard concentration of 0.1 M was utilized for subsequent studies.

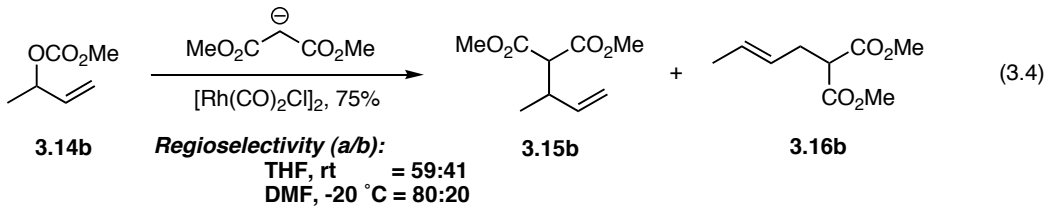
Table 3.3. Effect of Varying the Reaction Concentration on the $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Substitution Reaction of Carbonate **3.14a** with Sodiodimethyl Malonate

Entry	*Concentration [M] of 3.14a*	*Yield (%)*
1[b]	0.01	68
2	0.1	85
3[b]	0.5	<10

[a]Conditions: 2.5 equiv. of $CH_2(CO_2Me)_2$, 2.0 equiv. of NaH, THF, room temperature, 2-4 h. **3.15a/3.16a** = 97:3. [b]Reaction run for 24 h.

A serendipitous discovery was made when we analyzed the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation of the allylic carbonate **3.14b** (Eq. 3.4). Namely, when substrate **3.14b** was allowed to react with sodiodimethyl malonate in the presence of $[Rh(CO)_2Cl]_2$ at room temperature, a mixture (ca. 1:1) of regioisomeric products was obtained under the same conditions that had been used for carbonate **3.14a**. However, when the solvent was switched from THF to DMF and the temperature of the reaction was lowered to -20 ˚C, the ratio of **3.15b/3.16b** improved from 59:41 to 80:20 favoring the branched regioisomer **3.15b**. These results suggest that changing the solvent from THF to DMF increased the rate of nucleophilic attack by the malonate anion, so the reaction could be conducted at a lower temperature where the rate of *enyl* isomerization is suppressed. Oxidative addition of the metal catalyst followed by rapid nucleophilic attack prior to isomerization of the allylmetal intermediate results in the formal direct substitution product. By modifying the solvent and temperature of the reaction to

increase the rate of nucleophilic attack and slow the isomerization of metal-stabilized intermediates, the extent of regioisomeric leakage can be minimized.



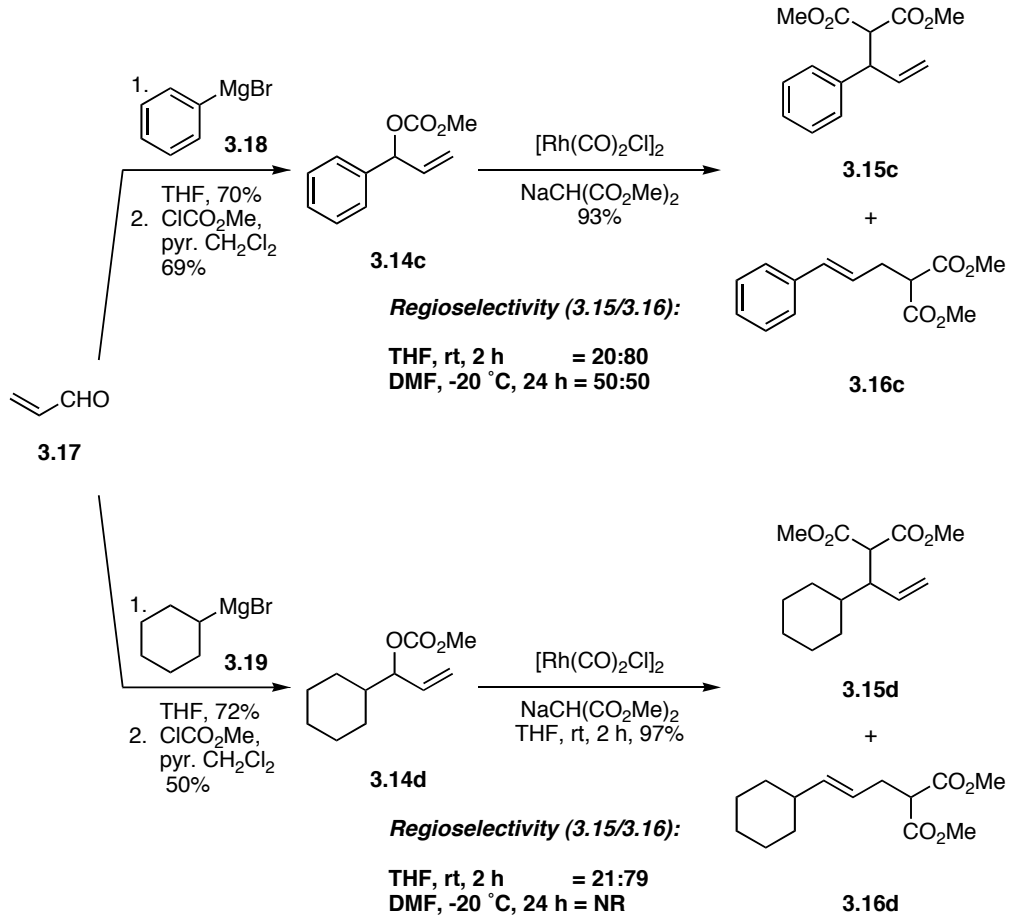
(3.4)

Although the ratio of regioisomers could be improved in the substitution of carbonate **3.14b**, we were perplexed that such poor regiocontrol was observed in comparison to the alkylation of **3.14a**. Additionally, the complete reversal of regioselectivity in the alkylation of cyclopropyl lactone **3.7** further piqued our curiosity. The allylic moiety in substrates **3.7** and **3.14b** both contained a terminal olefin, whereas the carbonate in **3.14a** was allylic to an internal 1,2-disbustituted carbon-carbon double bond. This observation led us to analyze the effect temperature and solvent would have on the regioselectivity in a series of other terminally substituted allyl substrates.

Toward this end, we studied the reaction of carbonate **3.14c**, which is commonly used in reactions promoted by numerous allylic alkylation catalysts (see Chapter 1). Allylic carbonate **3.14c** was synthesized in two steps from acrolein (**3.17**) by sequential addition of phenyl magnesium bromide (**3.18**) and acylation of the resulting carbinol (Scheme 3.3). When the allylic alkylation was performed at room temperature in THF, the formation of the linear regioisomer **3.16c**, resulting from substitution at the allylic carbon not bearing the leaving group, was observed. However, when the temperature of the reaction was lowered to –20 ˚C and the reaction was performed in DMF instead of THF, the ratio of **3.15c/3.16c** decreased to a 50:50 ratio.

The main structural difference between **3.14b** and **3.14c** is the benzylic nature of the carbonate moiety in compound **3.14c**. It is conceivable that the additional steric bulk of the phenyl group in **3.14c**, as compared to methyl, was a dominant factor in controlling the regioselectivity of the substitution reaction. However, conjugative stabilization of the phenyl ring, present only in the formation of **3.16c**, may also be a significant driving force. To test this hypothesis, we synthesized carbonate **3.14d** by reaction of cyclohexyl magnesium bromide (**3.19**) with acrolein followed by acylation of the resulting secondary carbinol. Treatment of allylic carbonate **3.14d** under the standard $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation conditions in THF at room temperature provided the linear product **3.16d** preferentially (regioselectivity = 79:21). However, carbonate **3.14d** failed to react with sodiodimethyl malonate in the presence of $[Rh(CO)_2Cl]_2$ when the alkylation reaction was performed in DMF at either 0 ˚C or –20 ˚C for extended time (>24 h). This result seems to suggest that the conjugative stabilization is not a significant determinant in the regiochemistry of the alkylation of **3.14c** and that steric factors might be more important.

Scheme 3.3



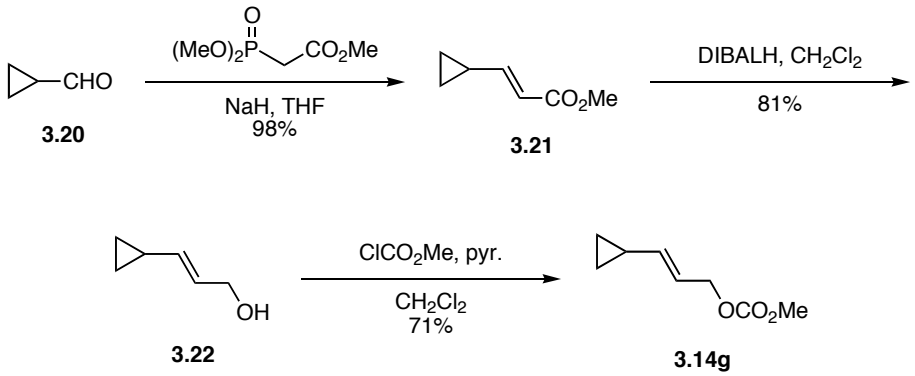
With the preliminary optimization of the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation complete, we were able to see that the reaction could proceed efficiently with 5 mol% catalyst loading at a concentration of 0.1M with respect to the starting carbonate. The solvent and temperature had a dramatic effect on the results obtained from the reaction. Although the reaction proceeded with good regioselectivity and with relatively short reaction times at room temperature in THF, the reaction was qualitatively much faster in DMF, which allowed the use of lower temperatures. Extending reaction times and lowering the temperature to –20 °C was found to improve the regioselectivity in the

substitution of allylic carbonates performed in DMF. However, THF was the solvent of choice because it was operationally easier to handle. Namely, those reactions run in DMF required an aqueous workup to remove the solvent, whereas those performed in THF could be filtered through a short plug of silica gel and the products isolated after flash column chromatography.

3.2.2 $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation of Unsymmetrical Primary Carbonates with Dimethyl Malonate

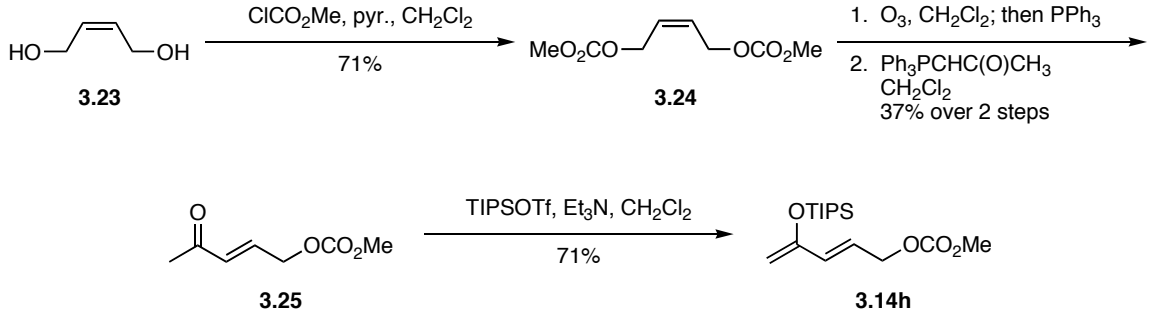
Having established a set of reaction conditions as a starting point, the scope of the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation using a number of allylic carbonates was examined. Preliminary results utilizing primary allylic carbonates in the substitution reaction are listed in Table 3.3. The synthesis of the requisite allylic substrates was straightforward. The methyl carbonates were obtained in one step from the corresponding allylic alcohols by reaction with methyl chloroformate and pyridine in CH_2Cl_2.[351] Yields for the acylation reactions were generally excellent. The corresponding allylic alcohol precursors to carbonates **3.14e-f** and **3.14i-k** were commercially available. The synthesis of carbonates **3.14g** and **3.14h** was straightforward as illustrated in Scheme 3.4. Thus, cyclopropyl aldehyde **3.20** was treated with the anion of trimethyl phosphonoacetate to provide the □,□-unsaturated ester **3.21** in 98% yield.[286] Subsequent reduction with DIBALH gave the desired allylic alcohol **3.22**, which gave the carbonate **3.14g** in 71% yield upon treatment with methyl chloroformate and pyridine.

Scheme 3.4



Carbonate **3.14h** was obtained in four steps from commercially available *cis*-2-butene-1,4-diol (**3.23**) (Scheme 3.5). Bisacylation of diol **3.23** with methyl chloroformate provided dicarbonate **3.24** in good yield. Ozonolytic cleavage of **3.24** followed by sequential treatment with PPh_3 and 1-triphenylphosphoranylidene-2-propanone gave the □,□-unsaturated ketone **3.25** in modest yield.[352] Silyl enol ether formation with TIPSOTf and Et_3N provided enol ether **3.14h**.

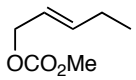
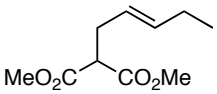
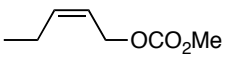
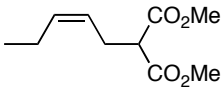
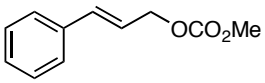
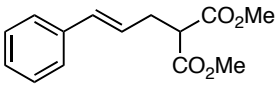
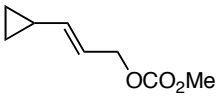
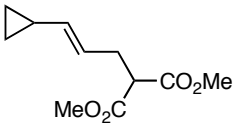
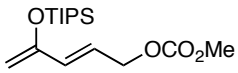
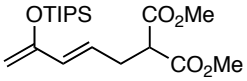
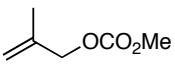
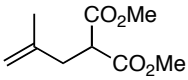
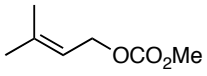
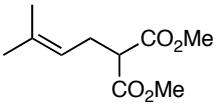
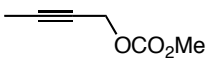
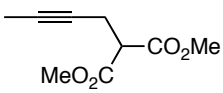
Scheme 3.5



Examination of the entries in Table 3.4 reveals that $[Rh(CO)_2Cl]_2$ catalyzed the facile and regioselective alkylations of various primary carbonates **3.14a-k** to provide the

corresponding substitution products **3.6a-k** selectively in each case.[353] The reactions typically proceeded with excellent regiocontrol that favored substitution at the carbon atom bearing the leaving group. A number of general trends and notable features merit additional discussion.

Table 3.4. Regioselectivity in the $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation of Unsymmetrical Primary Carbonates[a]

Entry	*Allylic Carbonate*	*Major Product*	*Yield[b] (%)*	*Ratio 3.15:3.16[c]*
1[d]	 **3.14a**	 **3.15a**	84	97:3
2[e]	 **3.14e**	 **3.15e**	86	99:1 (97:3)[i]
3[e]	 **3.14f**	 **3.15f**	93	90:10
4[e]	 **3.14g**	 **3.15g**	84	89:11
5[f]	 **3.14h**	 **3.15h**	94	97:3
6[f]	 **3.14i**	 **3.15i**	71	-
7[g]	 **3.14j**	 **3.15j**	75	92:8
8[e]	 **3.14k**	 **3.15k**	52	99:1

[a]Conditions: 5 mol% of $[Rh(CO)_2Cl]_2$, 2.5 equiv of $CH_2(CO_2Me)_2$, 2.0 equiv of NaH (2.0 eq.). [b]Isolated yields. [c]Ratios determined by GLC. [d]THF, rt. [e]THF, 0 °C. [f]DMF, rt. [g]DMF, -20 °C. [h]DMF, 0 °C. [i]Ratio of *cis*/*trans* isomers.

Primary allylic carbonates having internal disubstituted carbon-carbon double bonds provided primarily linear alkylation products (Entries 1–5). As discussed in Section 1.1.3.1 palladium catalysts exhibited this mode of regioselectivity. This is noteworthy as results outlined in Sections 1.B.4-1.B.7 illustrate that the opposite is typically observed for ruthenium, molybdenum, iridium and most rhodium catalysts.[5,12,19,354] The *Z*-carbonate **3.14e** (entry 2) underwent alkylation to provide the *less stable Z*-product with little carbon-carbon double bond isomerization. This is noteworthy because extensive *Z* → *E* isomerization of *Z*-allylic substrates is generally observed using other transition metal catalysts, although there are reports of *Z*-selective allylic substitutions of *Z*-substrates that are catalyzed by iridium,[91,100,101] palladium,[72,355,356] and tungsten.[357] The temperature and solvent were critical to maintaining the *Z*-double bond. For example, if the reaction was performed at room temperature, the mixture of *Z*/*E* isomers dropped to 86:13. However, if the reaction was run in DMF at temperatures ranging from room temperature to –20 °C, the *E*-isomer was obtained as the major product. This solvent effect was rather surprising because we believed that increasing the rate of nucleophilic attack, a phenomena that we observed by running the reaction in DMF, would lead to less isomerization of the double bond. Unfortunately, this had the opposite effect on *Z* → *E* isomerization. The reader is referred to Sections 1.1.3.3 and 1.1.5.2 for a discussion of double bond geometry in the transition metal-catalyzed allylic alkylation reaction.

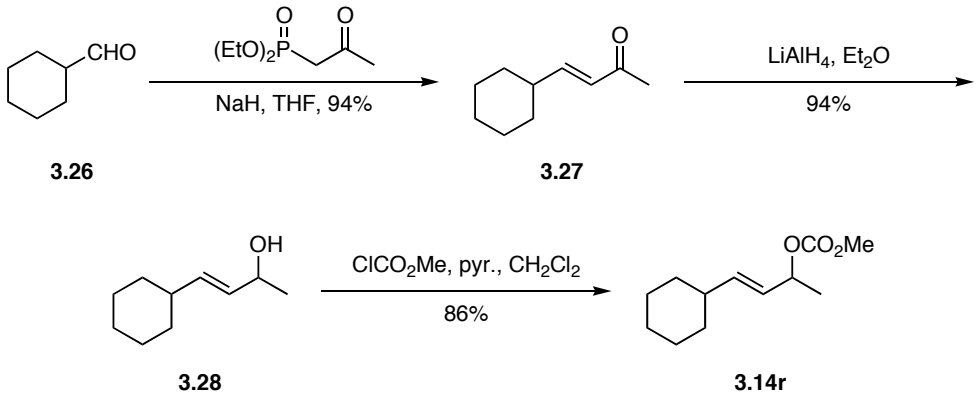
Allylic alkylation of carbonate **3.14f** provided the linear product **3.15f** with good regiocontrol. This result is significant because using molybdenum,[77] iridium[101] and ruthenium[104] catalysts, nucleophilic attack generally occurs at the more electrophilic benzylic site. The presence of sensitive enol ethers in conjugation with the allylic subunit did not adversely affect the regiochemistry or efficiency of the reaction as illustrated by

the alkylation of carbonate **3.14h** (entry 5). It is thus evident that additional functional handles can be present for manipulations consequent to the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation. As illustrated by the alkylation of carbonate **3.14i**, internal substitution does not affect the efficiency of the alkylation, as malonate **3.15i** was isolated in 71% yield (entry 6). That **3.14j** (entry 7) underwent *any* alkylation is noteworthy because 2,3,3-trisubstituted allylic carbonates are inert to the modified Wilkinson's catalyst reported by Evans and typically require forcing conditions with other transition metal catalysts.[106,277,358] Finally, $[Rh(CO)_2Cl]_2$ may be used effectively to catalyze the alkylation of propargylic carbonates to give substituted alkynes with none of the allenic product commonly observed in palladium catalysis (Entry 10).[359]

3.2.3 $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation of Unsymmetrical Secondary and Tertiary Carbonates with Dimethyl Malonate

The reaction scope was further extended to include secondary and tertiary allylic carbonates, as illustrated by the results in Table 3.5. The allylic carbonates were readily synthesized from their corresponding allylic alcohols by reaction with methyl chloroformate in the presence of pyridine. The allylic alcohol precursors for carbonates **3.14l-n** and **3.14p** and allylic acetate **3.14o** were commercially available. However, allyl carbonate **3.14q** was synthesized by the addition of methylmagnesium bromide to 2-pentenal followed by acylation with methyl chloroformate.[360] Also, carbonate **3.14r** was synthesized in a three-step sequence as illustrated in Scheme 3.6.[361] Horner-Wadsworth-Emmons olefination of cyclohexane carboxaldehyde (**3.26**) provided □,□-unsaturated ketone **3.27** in 94% yield. Reduction of **3.27** with $LiAlH_4$ gave allylic alcohol **3.28**, which was subsequently acylated under standard conditions to form allylic carbonate **3.14r** in 86% yield.

Scheme 3.6



Allylic carbonate **3.14s** was synthesized in two steps from commercially available cyclohexyl bromide (**3.29)** by generation of the corresponding Grignard reagent followed by nucleophilic addition to crotonaldehyde (**3.30**) (Scheme 3.7). The resulting allylic alcohol **3.31** was then acylated under standard conditions to provide allyl carbonate **3.14s**.

Scheme 3.7

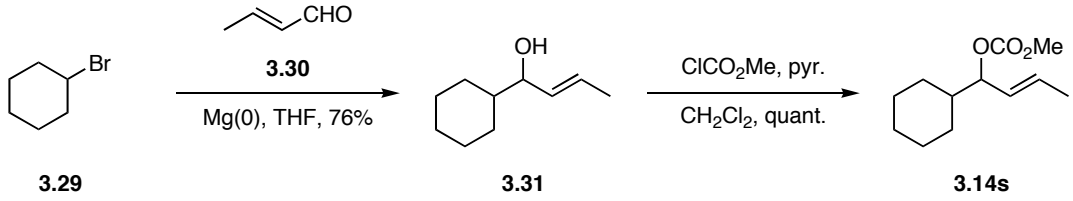
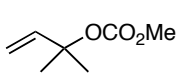
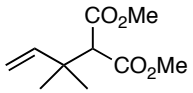
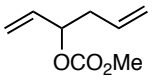
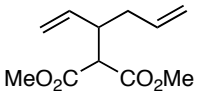
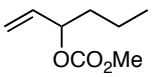
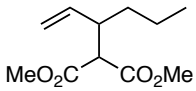
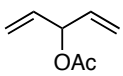
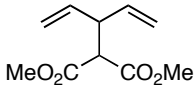
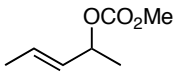
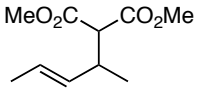
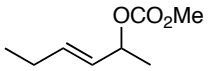
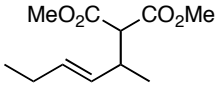
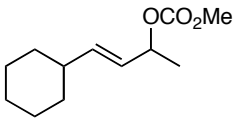
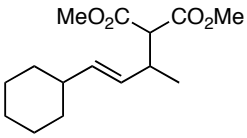
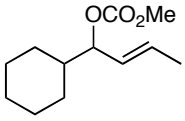
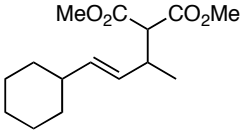


Table 3.5. $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation of 2° and 3° Carbonates[a]

Entry	*Allylic Carbonate*	*Major Product*	*Yield (%)*	*Ratio 3.16:3.17*
1[e]	 **3.14l**	 **3.15l**	80	94:6
2[e]	 **3.14m**	 **3.15m**	89	91:9
3[d]	 **3.14n**	 **3.15n**	80	60:40
4[e,j]	 **3.14o**	 **3.15o**	74	96:4
5[d]	 **3.14p**	 **3.15p**	89	–
6[h]	 **3.14q**	 **3.15q**	88	96:4
7[e]	 **3.14r**	 **3.15r**	94	93:7
8[h]	 **4.14s**	 **4.16s**	94	93:7

[a]Conditions: 5 mol% of $[Rh(CO)_2Cl]_2$, 2.5 equiv of $CH_2(CO_2Me)_2$, 2.0 equiv of NaH (2.0 eq.). [b]Isolated yields. [c]Ratios determined by GLC. [d]THF, rt. [e]THF, 0 °C. [f]DMF, rt. [g]DMF, -20 °C. [h]DMF, 0 °C. [i]Ratio of *cis*/*trans* isomers. [j]The corresponding carbonate was unstable.

Although a quaternary center was generated in the process, the isomeric tertiary allylic carbonate **3.14i** underwent facile substitution to provide the product **3.15i** (Table 3.5, entry 1) with excellent regioselectivity. The differences in reactivity of $[Rh(CO)_2Cl]_2$ and other catalysts capable of promoting allylic substitutions is underscored by the preliminary results obtained with secondary allylic carbonates and acetates **3.14m-s** (Entries 2–8). In each case, formal direct displacement of the leaving group is the dominant reaction pathway. When the substrate contained additional unsaturation, which in the case of carbonate **3.14m** renders the leaving group homoallylic as well as allylic, the substitution product **3.15m** was obtained in good yield (89%) and regioselectivity (91:9) (Entry 2). However, when the terminal double bond is absent as in **3.14n**, the regiocontrol in the reaction suffers, providing only a 60:40 ratio of substitution products **3.15n** and **3.16n** in THF at room temperature (entry 3). When the alkylation of **3.14n** was performed in DMF at lower temperature (*i.e.* –20 ˚C to room temperature) no improvement in the regiocontrol was observed.

It has been observed that pendant olefins can direct the regiochemistry of the transition metal-catalyzed allylic alkylation reactions, presumably *via* a weak coordination of carbon-carbon double bond to the metal.[362] This additional directing effect may be one reason for the enhanced regiocontrol observed in the reaction of **3.14m** (entry 2) in an otherwise problematic substrate. This general trend of formal direct substitution holds even when conjugation would favor substitution at the opposite allylic terminus as illustrated by the reaction of carbonate **3.14o** to provide the branched substitution product **3.15o** (entry 4). Entries 6 and 7 illustrate the efficiency of the $[Rh(CO)_2Cl]_2$-catalyzed allylic substitution reaction in which electronic factors are not present to aid in directing the regioselectivity of the alkylation.

When substrate **3.14s** was treated with the sodium enolate of dimethyl malonate in the presence of $[Rh(CO)_2Cl]_2$, the substitution product **3.16s**, which resulted from S_N2'-*like* alkylation was obtained as the major product in a 93:7 ratio of regioisomers. This result stands in stark contrast with what was observed when carbonate **3.14r** was alkylated under the same conditions. Apparently the observed "memory effect" was not strong enough to overcome what could be the increased steric demand by the branching on the cyclohexyl group. Given the drastically different the regiochemical outcomes associated with the alkylation of carbonates **3.14r** and **3.14s**, it appears that branching on the carbon one atom removed from the allyl moiety imparts a particularly strong influence on the outcome of the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation. This effect is apparently more pronounced than even that observed when the substitution on the three allylic carbons themselves is increased.

Although understanding the steric interactions between the catalyst, allylic substrate and the nucleophile is critical to gaining insight into regiochemical trends, electronic factors are also known to influence the regiochemistry, and much be considered. If one compares the results obtained when carbonate **3.14d** and **3.14s** are treated with sodiodimethyl malonate in the presence of $[Rh(CO)_2Cl]_2$, steric effects do not adequately explain the regioselectivities observed. Based upon steric effects alone, one would expect that malonate **3.16d** should be formed with higher selectivity (79:21) than **3.16s** (97:3). These results seem to suggest a contributing electronic influence in the regiochemistry as has been observed with molybdenum, tungsten, iridium and Evan's modified Wilkinson's catalyst system (see Chapter 1.B). Regiochemical leakage in the formation of **3.16d** results from electronic preference for alkylation to occur at the secondary allylic carbon, a factor not present in the allylmetal intermediate formed by ionization of carbonate **3.14s**.

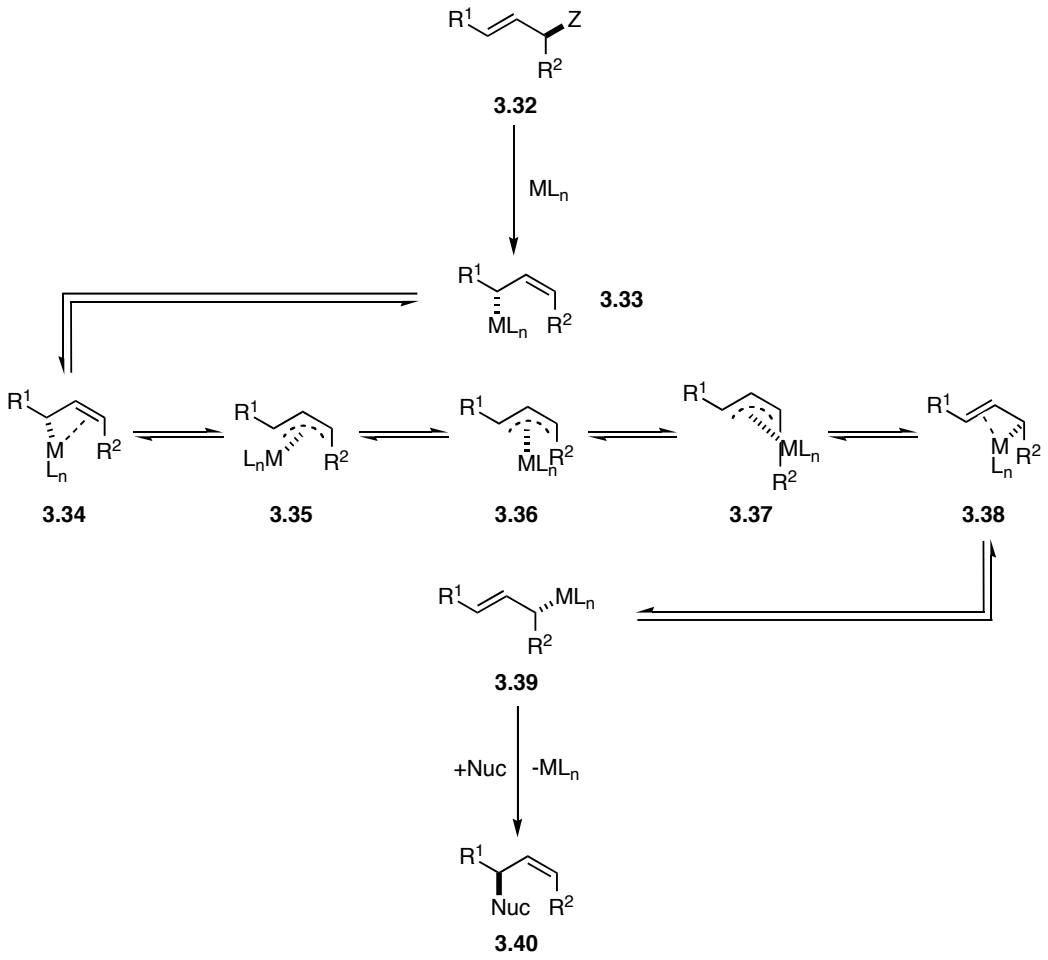
3.2.4 Summary of the Regiochemical Trends Observed in the Alkylation of Simple Allylic Carbonates with Dimethyl Malonate Catalyzed by $[Rh(CO)_2Cl]_2$

That $[Rh(CO)_2Cl]_2$ catalyzes the allylic alkylations of unsymmetrical substrates to give products in which substitution occurs at the carbon atom bearing the leaving group may be regarded as a "memory effect". Such phenomena have been examined in palladium-catalyzed allylic alkylations of enantioenriched and racemic secondary allylic substrates having the *same* number of substituents on the allyl moiety.[363] The nature of the memory effect observed in $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations thus differs significantly from those previously studied because the termini of the allylic moieties are *unequally* substituted. Mechanistic studies must be conducted to understand the origin of the regiochemistry in $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations and why it differs from analogous reactions promoted by other transition metal catalysts. Of particular interest in this regard is whether the rhodium-stabilized allyl intermediate resembles one of two σ-bonded metal species **3.33** or **3.39**, the (σ+π) *enyl* complexes **3.34** or **3.38**, as suggested by Evans in the modified Wilkinson's catalyst mediated allylic alkylations, or one of the other possible distorted η^3-allyl variant **3.35-3.37** (Scheme 3.8).[106]

The regioselectivity of the allylic alkylation is dependent on the relative concentration of each intermediate and the rate of equilibration. If equilibration is rapid, the product distribution should arise from the most stable allylmetal intermediate. However, if equilibration is slow, the regiochemical ratios should mirror the structure of the starting material providing products resulting from a formal direct substitution. Unfortunately, determining where this equilibrium lies is not necessarily a simple endeavor. Qualitative analysis of the data obtained from the alkylation of a number of allylic substrates can provide an indication in most cases which of these allylmetal intermediates is dominant. However, if the metal-bound allyl species can be

recrystallized, and its structure determined by X-ray analysis, a more accurate picture of the reaction intermediate can be attained.

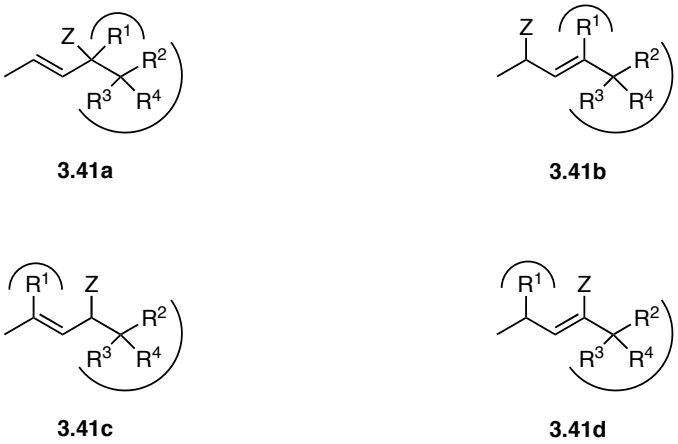
Scheme 3.8



To the best of our knowledge, this level of regioselective dependence on homoallylic substitution with respect to the starting allylic carbonate, while seemingly independent of the steric environment associated with the allylic moiety itself, has not been extensively explored. To clarify, if one considers the four possible allylic carbonates **3.41a-d** as depicted in Figure 3.1 there exists the allylic two sphere and

homoallylic sphere of steric influence represented by the allylic substituent R^1 and the homoallylic substituents R^2-R^4 respectively (Figure 3.1). In cases we examined (Scheme 3.3, Table 3.2, entry 8) It appears as though if the homoallylic sphere is large (R^2, R^3 or $R^4 \neq H$) alkylation is directed to the opposite allylic terminus. However, if R^2-R^4 = H substitution occurs at the carbon where the leaving group Z resided, regardless of the steric bulk of R^1. Typically, if the regiochemistry of a transition metal-catalyzed allylic alkylation is influenced by the steric environment around the homoallylic centers of the starting carbonate, than a similar effect is observed as the steric congestion on the allylic carbons is likewise altered.[7,83,104] However, for the regiochemical outcome to be seemingly independent of the allylic sphere while the homoallylic sphere has a profound steric effect on the outcome is particularly unique.

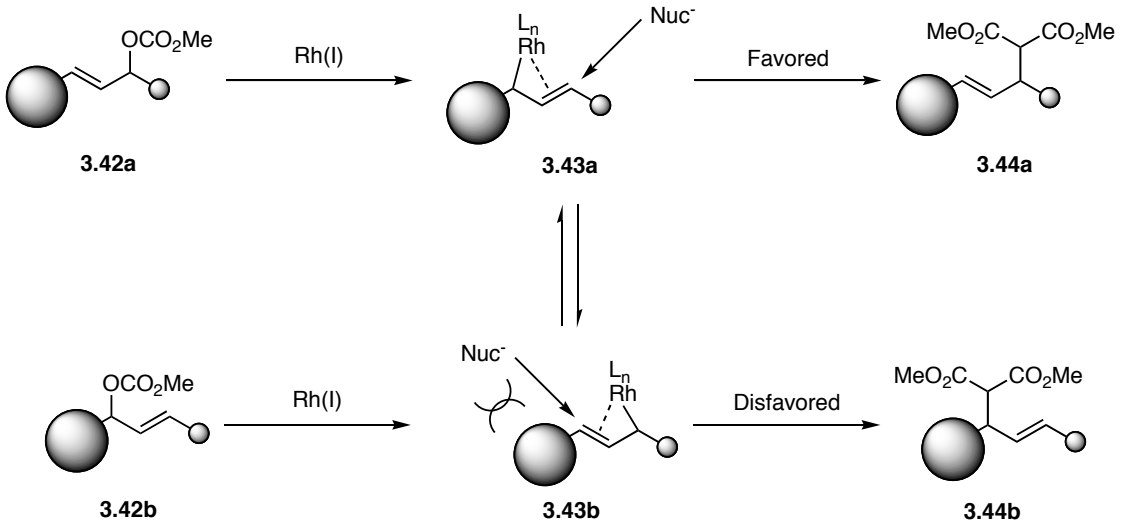
Figure 3.1. Relative influence of allylic and homoallylic substitution on regioselectivity.



To summarize the observations we have made up to this point, Scheme 3.9 provides a graphical representation of how initial oxidative addition of the rhodium(I) complex provides allylmetal variants **3.43a** and **3.43b** from the corresponding starting allylic carbonates **3.42a** and **3.42b**. Nucleophilic attack at the less hindered allyl

terminus of intermediate **3.43a** yields the alkylation product **3.44a**, which corresponds to the product of substitution at the carbon bearing the leaving group. Nucleophilic attack in a similar fashion on **3.43b** would be expected to be relatively slow due to the steric interactions between the large substituents attached to the allylic substrate and the attacking nucleophile. When nucleophilic attack is slowed, □-□-□ isomerization can produce the intermediate **3.43a**. This isomerization could then lead to preferential formation of **3.44a** as observed for carbonate **3.14s** (Table 3.5, entry 8). The steric effect from substituents in these examples is strikingly absent from entries 1-4 in Table 3.5 where differing substitution is present directly on the allyl moiety. The lack of influence these substituents seem to impart on the product distribution may arise as a function of their proximity to the angle of nucleophilic attack. Although we are unfamiliar with studies addressing this issue, the steric environment around the homoallylic carbon of the starting carbonate may be more in line with the path of anion addition depending upon the nature of the metal stabilized complex. This discussion is purely speculative at this point as studies have not been conducted to determine the validity of this hypothesis. The absence of reports describing a similar phenomena of such steric influence on the regioselectivity with other transition metals known to catalyze allylic alkylations warrants further exploration in the reaction catalyzed by $[Rh(CO)_2Cl]_2$.

Scheme 3.9

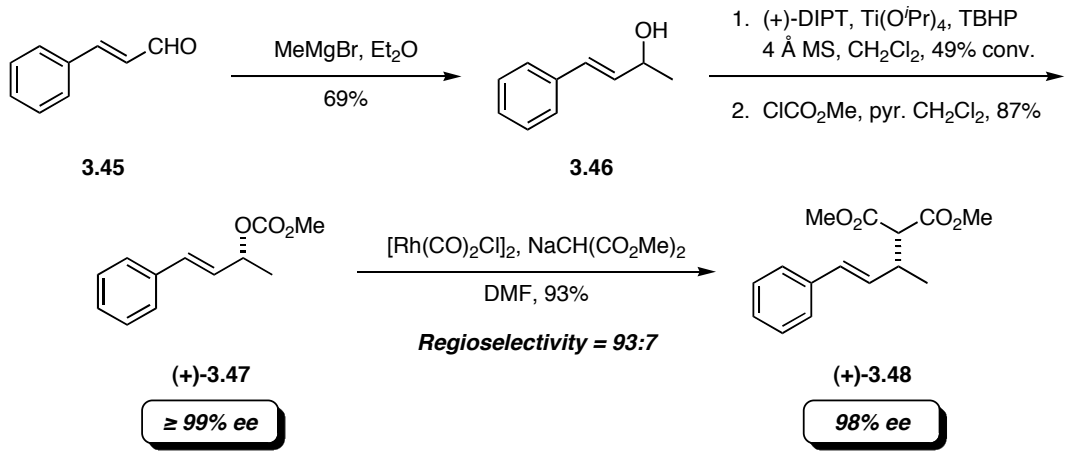


3.2.5 Conservation of Absolute Stereochemistry in the $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation of Enantioenriched Secondary Allylic Carbonates

In order to determine the stereochemical outcome of $[Rh(CO)_2Cl]_2$-catalyzed allylic substitutions, enantioenriched allylic carbonate **(+)-3.47** was synthesized in three steps from cinnamaldehyde (**3.45**) to determine if the reaction proceed with net inversion, net retention or racemize the starting carbonate (Scheme 3.10). Addition of methyl magnesium bromide to aldehyde **3.45** provided the corresponding racemic alcohol **3.46** in 69% yield. Subjecting alcohol **3.46** to Sharpless kinetic resolution[364] followed by acylation of the enantioenriched alcohol under standard conditions, afforded the allylic alkylation precursor **(+)-3.47** in ≥99% *ee* (Scheme 3.8). The enantiomeric excess of carbonate **(+)-3.47** was determined by chiral HPLC and the absolute configuration ascertained by comparison of the optical rotation to literature values. When allylic carbonate **(+)-3.47** was treated with the sodium salt of dimethyl malonate in the presence

of $[Rh(CO)_2Cl]_2$, malonate **(+)-3.48** was obtained in 93% yield and 98% *ee* (regioselectivity = 93:7). The enantioselectivity of the allylic alkylation was determined by chiral HPLC analysis of malonate **(+)-3.48** whose optical rotation was compared to literature values to obtain the absolute configuration. Based upon these experiments, $[Rh(CO)_2Cl]_2$ appears to catalyze substitutions of secondary allylic carbonates with net retention of configuration as has been observed with Pd,[5,12,13] Ru,[104] Mo,[75] Rh[106] and Ir[101] catalysts. However, whether the reaction proceeds *via* an *anti-anti* or *syn-syn* mechanistic pathway has not yet been determined.

Scheme 3.10

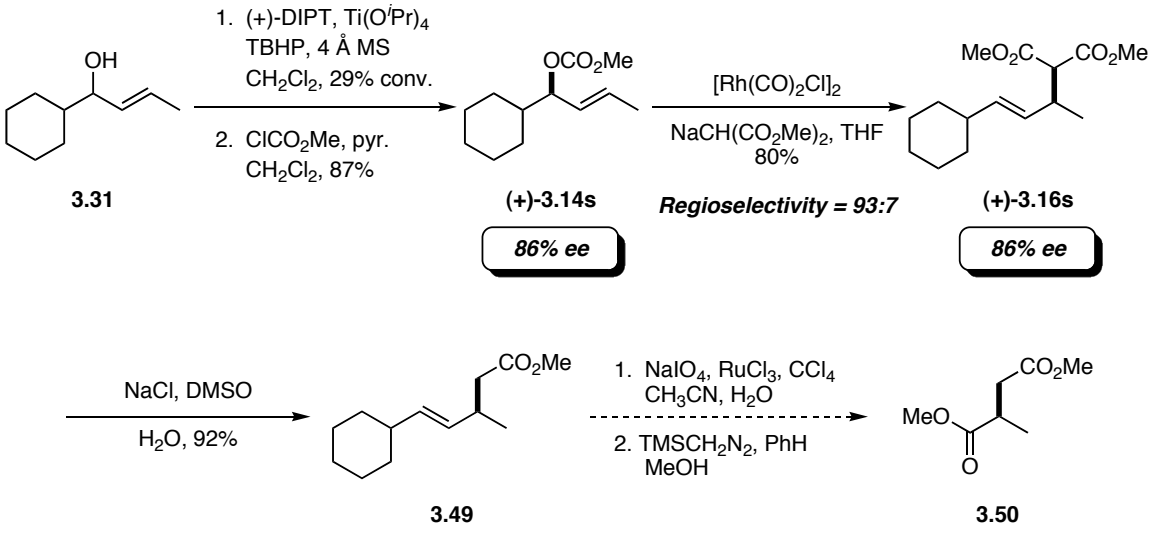


At this point we became interested in determining the stereochemical outcome of the $[Rh(CO)_2Cl]_2$-catalyzed substitution reaction in the rare case where the formal indirect substitution product was obtained preferentially. To that end, known enantioenriched carbonate **(+)-3.14s** was obtained in 86% *ee*, which was determined by chiral HPLC analysis, *via* Sharpless kinetic resolution of the corresponding allylic alcohol **3.31** followed by acylation with methyl chloroformate (Scheme 3.11). The absolute configuration of **(+)-3.14s** was confirmed by comparison of the optical ration to

known literature values.[364] Alkylation of **(+)-3.14s** under the same conditions established for **3.14s** yielded the substitution product **(+)-3.16s** with complete conservation of optical purity, as determined by chiral HPLC.

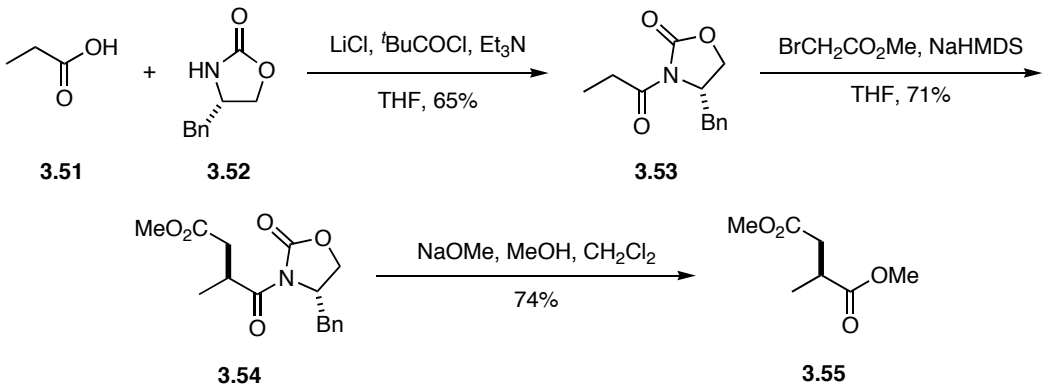
In order to determine the absolute stereochemistry of **(+)-3.16s**, we first attempted to obtain an X-ray crystal structure of a chiral amine salt derived from the corresponding monocarboxylic acid that was formed by ester hydrolysis and subsequent decarboxylation. Unfortunately, crystals suitable for X-ray analysis proved elusive, and we therefore resorted to transforming **(+)-3.16s** into diester **3.50**, whose enantiomer **3.55** was synthesized independently from propanoic acid (**3.51**)[365] (Scheme 3.12). By comparing the optical rotations of esters **3.50** and **3.55** the absolute configuration of **(+)-3.16s** could be elucidated. Thus, Krapcho decarboxylation[366] of **(+)-3.16s** provided monoester **3.49**. Subsequent oxidative cleavage followed by esterification utilizing trimethylsilyl diazomethane should provide diester **3.50**.

Scheme 3.11



The diester **3.55** was synthesized starting from propanoic acid (**3.51**). Installation of chiral oxazolidinone **3.52** under standard conditions provided imide **3.53** in 65% yield (Scheme 3.12). Diastereoselective alkylation with methyl bromoacetate provided ester **3.54** in 71% yield. Subsequent cleavage of the chiral auxiliary with sodium methoxide in methanol provided the diester **3.55**.[366] By comparing the optical rotations for diesters **3.50** and **3.55**, we should be able to confirm that although the regiochemistry of the alkylation reversed itself, the overall stereochemical outcome remained the same.

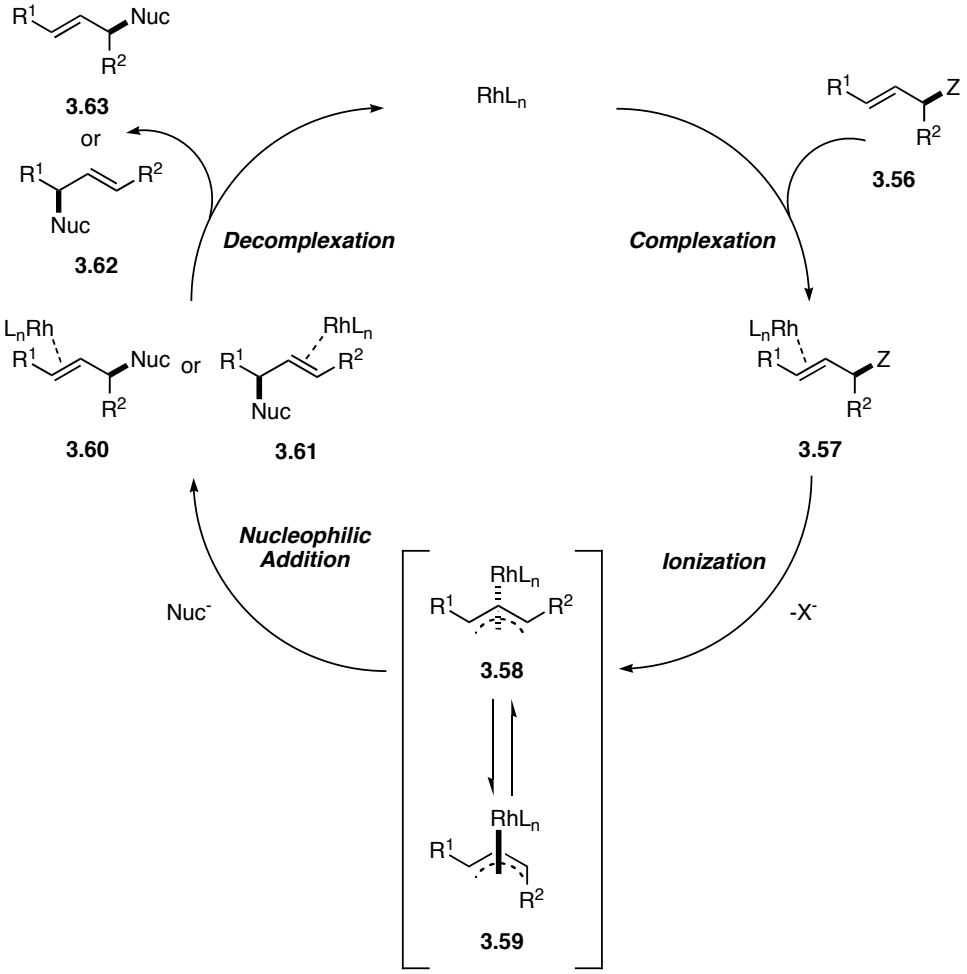
Scheme 3.12



Thus, the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation proceeded with retention of stereochemistry irrespective of the regiochemical consequence of the alkylation. This result is in accord with the facial selectivity previously observed with transition metal-catalyzed allylic alkylations. It is important to note that although the allylic alkylation reaction catalyzed by $[Rh(CO)_2Cl]_2$ proceeds stereoselectively, one can draw either an *anti-anti* or *syn-syn* mechanistic possibility to explain this result. For brevity, the *anti-anti* pathway will be discussed at this time. As illustrated in Scheme 3.13, treatment of allylic substrate **3.56** with the transition metal catalyst, initial complexation yields **3.57**, which then undergoes oxidative addition from the opposite face of the allyl system than

the leaving group Z. Formation of allylmetal intermediate **3.58** can then undergo racemization, presumably *via* an η^3-η^1-η^3 isomerization pathway to yield intermediate **3.59**. The fact that we do not see an appreciable loss of enantiopurity and that absolute stereochemistry is conserved throughout the course of the reaction, suggests that this racemization is slow or does not occur at all. Subsequent addition of the nucleophile in this case provides the metal-complexed regioisomeric substitution products **3.60** and **3.61**, which upon decomplexation, yield products **3.62** and **3.63** without loss of enantiopurity. The overall result of this metal-catalyzed allylic alkylation is retention of stereochemistry *via* an *anti-anti* mechanistic pathway. Although most transition metal catalysts are believed to proceed by the mechanism illustrated in Scheme 3.13,[68] the molybdenum-catalyzed process transfers stereochemical identity *via* a double retention pathway.[89,90] Whether or not $[Rh(CO)_2Cl]_2$-catalyzed substitutions proceed by an *anti-anti* or *syn-syn* mechanism, the π-allyl intermediates would likewise be of the same relative structure in order to yield the observed products without loss of enantiomeric purity. Therefore, isomerization from **3.58** to **3.59**, or vice versa, would presumably be slow relative to nucleophilic addition.

Scheme 3.13

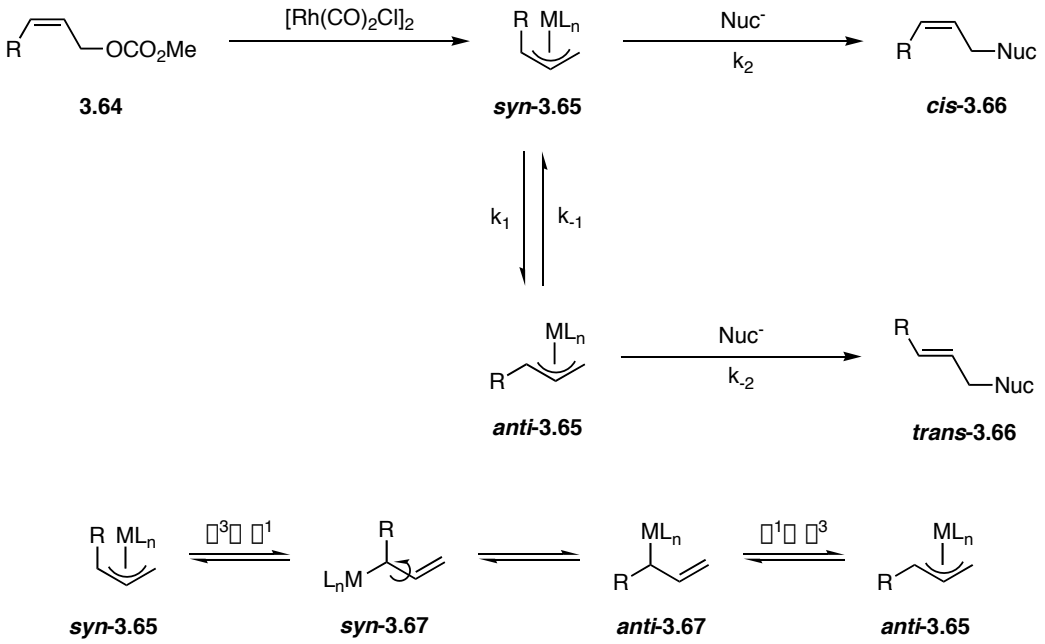


3.2.6 The Scope with which the *Z*-Geometry is Maintained in the $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation of *Z*-Allyl Carbonates

It has been well established that olefin geometry in transition metal-catalyzed allylic alkylations is not easy to control for systems in which both isomers are on an equal energetic footing, or the desired configuration is actually the less stable of the two (see Chapter 1.B). This is lack of command is prevalent in the allylic alkylations of substrates

with *cis* carbon-carbon double bonds. Most transition metals will isomerize the *Z*-olefin to provide the more stable *E*-isomeric substitution product, as was discussed in Chapter 1. The plausible mechanistic pathway by which this may occur is illustrated in Scheme 3.13.[10] Complexation of the catalyst to the *Z*-olefin in substrate **3.64** is followed by the subsequent ionization step, and the ***syn*-3.65** π-allyl complex is formed. There exists an unfavorable interaction in ***syn*-3.65** between R and the metal center with its ligands. Isomerization of ***syn*-3.65** can presumably occur *via* an η^3-η^1-η^3 isomerization pathway to yield the thermodynamically more stable ***anti*-3.65**. Nucleophilic attack onto ***syn*-3.65** provides the corresponding *Z*-substitution product ***cis*-3.68**, whereas addition of the nucleophile to ***anti*-3.65** yields the isomeric alkylation product ***trans*-3.66**. Therefore, the relative ratio of *cis* to *trans* products can be correlated to the relative rates of nucleophilic attack on the metal-stabilized η^3-allyl complexes ***syn*-3.65** and ***anti*-3.65** (k_2 and k_3) and the rate of *syn*/*anti* isomerization (k_1/k_{-1}). Therefore, if nucleophilic attack on ***syn*-3.65** is faster than isomerization to ***anti*-3.65** ($k_2>k_1$) the olefin geometry will be conserved; otherwise loss of double bond character will be observed. Given that *Z* η^3 η^1 isomerization occurs readily with the majority of allylic alkylation catalysts, it would be advantageous for a new catalyst that mediates this transformation to be capable of maintaining olefin geometry.

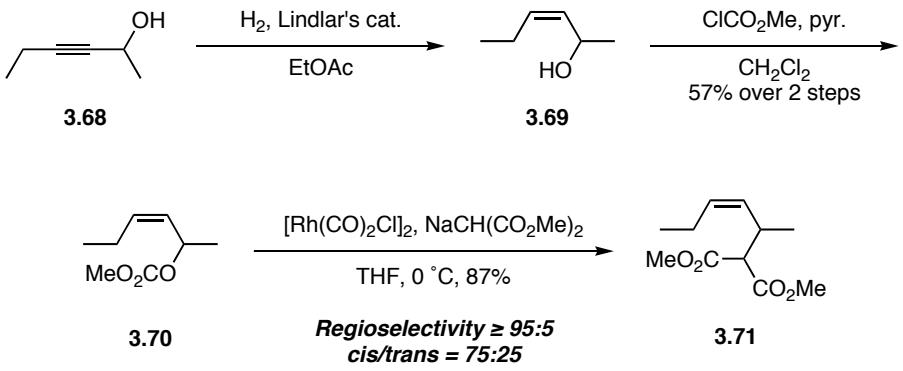
Scheme 3.14



Given the excellent *Z*-selectivity observed with allylic carbonate **3.14e** (Table 3.4, entry 2), we examined the scope of this olefin selectivity. To this end, secondary *Z*-allylic carbonates and more sterically congested nucleophiles (*i.e.* sulfones) were scrutinized for their propensity to provide *Z*-selective allylic alkylations. In an attempt to answer the first of these two queries, *Z*-allylic carbonate **3.70** was synthesized in two steps from propargyl alcohol **3.68** as illustrated in Scheme 3.15. Partial reduction of the alkyne **3.68** utilizing Lindlar's catalyst in EtOAc under an atmosphere of H_2 provided *cis*-allyl alcohol **3.69**. Subsequent acylation of **3.69** under the standard conditions gave the desired allyl carbonate **3.70** in 57% yield over the two steps. Treatment of substrate **3.70** with the sodium salt of dimethyl malonate in either THF or DMF at reaction temperatures ranging from room temperature to −20 °C was either too sluggish, resulting in ≥80% recovered starting material, or yielded malonate **3.71** with excellent regioselectivity (≥95:5), but extensive *cis* → *trans* isomerization (in THF at –20 °C). The loss of olefin

integrity observed with carbonate **3.70** may be due to the decreased rate of nucleophilic addition as a result of the increased steric environment around the electrophilic site of alkylation in comparison to the primary *Z*-allyl carbonate **3.14e**.

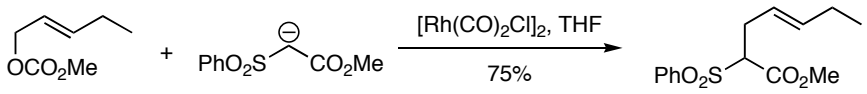
Scheme 3.15



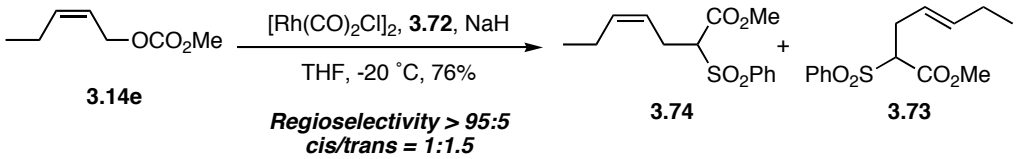
If steric factors are in fact the reason why alkylation of carbonate **3.70** proceeded with only moderate *cis*/*trans* selectivity, then increasing the steric bulk associated with the nucleophile would, likewise slow the rate of nucleophilic attack to the allylic center, resulting even in greater loss of olefin integrity. To answer this question we analyzed the affect a more sterically demanding such as methyl phenyl sulfonylacetate (**3.72**).

In order to establish first whether sulfones were even viable nucleophiles in $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations, carbonate **3.14a** was treated with the sodium salt **3.72** in the presence of $[Rh(CO)_2Cl]_2$ and the alkylation product **3.73** was obtained in 75% yield and with excellent regioselectivity (99:1) (Eq. 3.5). Satisfied with this result, *Z*-allyl carbonate **3.14e** was treated with the sodium anion of phenylsulfone **3.71** in the presence of $[Rh(CO)_2Cl]_2$ to provide a mixture of carbon-carbon double bond isomers **3.73** and **3.74** with excellent regioselectivity and good yield (Eq. 3.6). Unfortunately, there was extensive loss of olefin integrity as is reflected by the ratio (1.5:1) of **3.73** to **3.73.** These results, in conjunction with those illustrated in Scheme 3.16, seem to

indicate that in the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation reaction, maintaining olefin geometry during the reaction depends not only on the relative size of the nucleophile, but also on the substitution of the allylic carbon at which substitution will occur. Therefore, the results suggest that as the rate of nucleophilic attack (k_2 or k_3) slows, *syn-anti* isomerization (k_1/k_{-1}) becomes more important, and erosion in the stereoselectivity of the process occurs (Scheme 3.14).



3.14a **3.72** ***Regioselectivity = 99:1*** **3.73** (3.5)



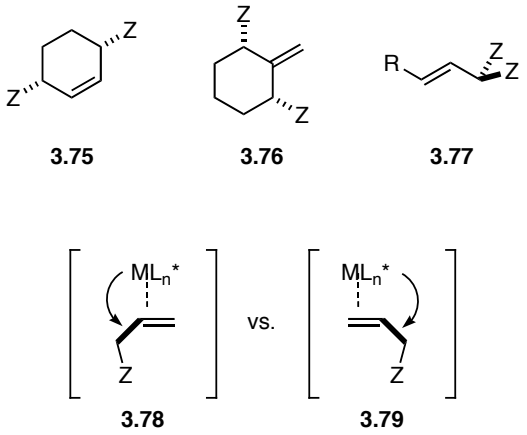
3.14e ***Regioselectivity > 95:5*** ***cis/trans = 1:1.5*** **3.74** **3.73** (3.6)

3.2.7 Attempts at Developing an Asymmetric $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation

Based on previous work involving $[Rh(CO)_2Cl]_2$-catalyzed asymmetric transformations,[270] we were interested in determining whether asymmetric induction could be obtained by the presence of chiral ligands during the allylic alkylations of racemic carbonates. The goal of this effort would be to start with a substrate whose electrophilic site is sp^3 hybridized and yield a substitution product where there is minimal loss of chemical yield and good enantioselectivity. In order for this to occur, either the initial ionization of the allylic substrate by the metal catalyst or the nucleophilic attack must be enantiodiscriminating. To avoid losing material in a kinetic resolution, *meso*-

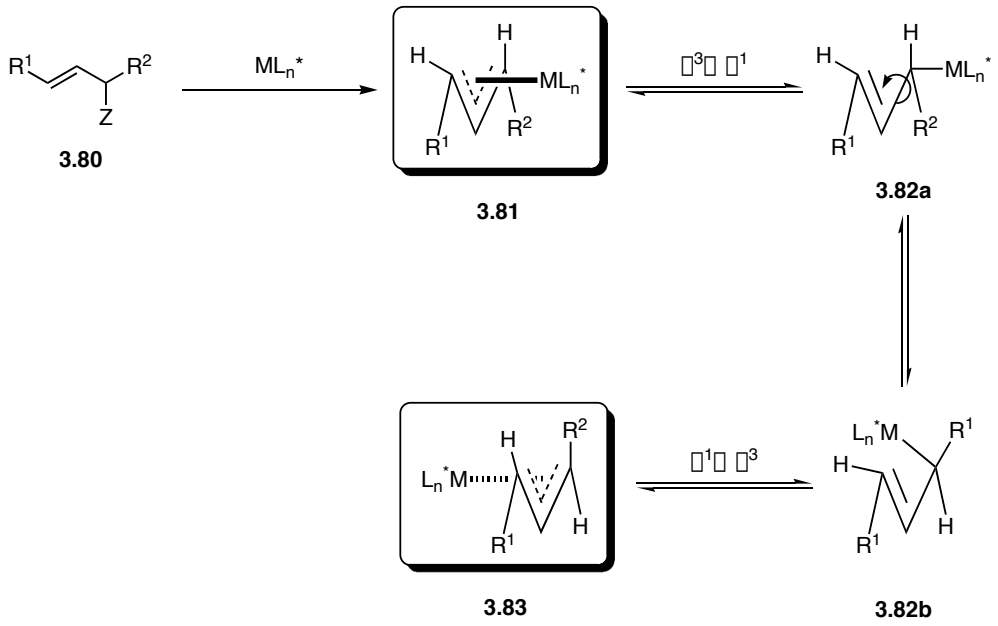
substrates **3.75-3.77** are typically employed to provide a synthetically useful method in which the enantiodetermining step involves facial discrimination of the olefin in metal complexed intermediates **3.78** and **3.79** and the maximum yield is 100 % (Figure 3.1).[13]

Figure 3.2. Substrate types for enantioselective allylic alkylations

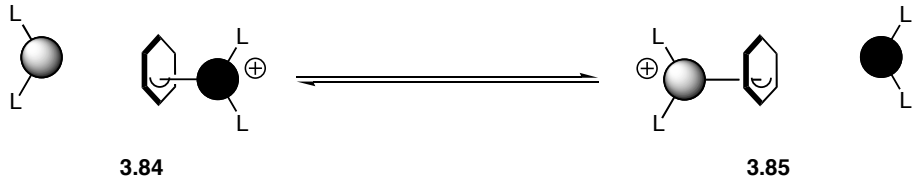


Unsymmetrical allylic substrates such as **3.80** can also be used for such asymmetric allylic alkylations, but the enantiofacial exchange of η^3-allyl transition metal-bound intermediates **3.81** and **3.83** must be possible (Scheme 3.16). This exchange is usually believed to occur through the η^3-η^1-η^3 isomerization sequence **3.82a** ⇌ **3.82b**. Alternatively, diastereofacial exchange may occur *via* a pathway in which a π-allylmetal species as **3.84** is transferred from one palladium complex to another to form **3.85** (Scheme 3.17). The exact mechanism for this process is uncertain, but it has been observed that isomerization can be inhibited by the presence of halide ions, low palladium(0) concentration, or through the use of bidentate ligands.[367] By one of the two mechanisms illustrated in Schemes 3.16 and 3.17, cyclic or unsymmetrical allyl systems can yield substitution products in good yields and with synthetically useful enantioselectivity.[13]

Scheme 3.16

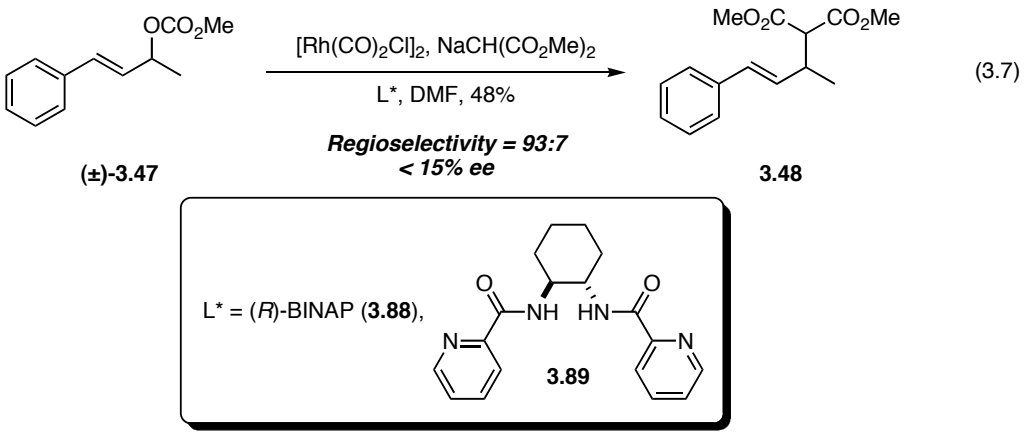


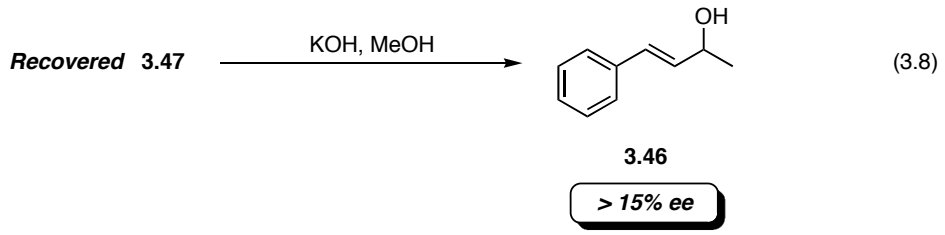
Scheme 3.17



To determine whether the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation conditions could be modified so that the process could be rendered enantioselective, the reaction was conducted with racemic carbonate **(±)-3.47** in the presence of an added chiral ligand (Eq. 3.7). Two ligands, (*R*)-BINAP (**3.86**) and Trost's diamide **3.87**, were chosen for initial examination. Unfortunately, best result was obtained with **3.87** to provide malonate **3.48** with low enantioselectivity (15% *ee*), as determined by chiral HPLC, in a mere 48% yield. To determine whether this method could be modified to achieve a kinetic

resolution of racemic carbonates, the recovered starting carbonate **3.47** was hydrolyzed with KOH in MeOH, and the optical purity of the resulting alcohol **3.46** was analyzed by chiral HPLC (Eq. 3.8). To our dismay, minimal enantiomeric excess was observed (< 15% ee). However, the realm of asymmetric allylic alkylations using $[Rh(CO)_2Cl]_2$ remains attractive, and therefore a screening of ligands, reaction conditions and analyzing *meso* allylic carbonates are avenues that offer future potential.





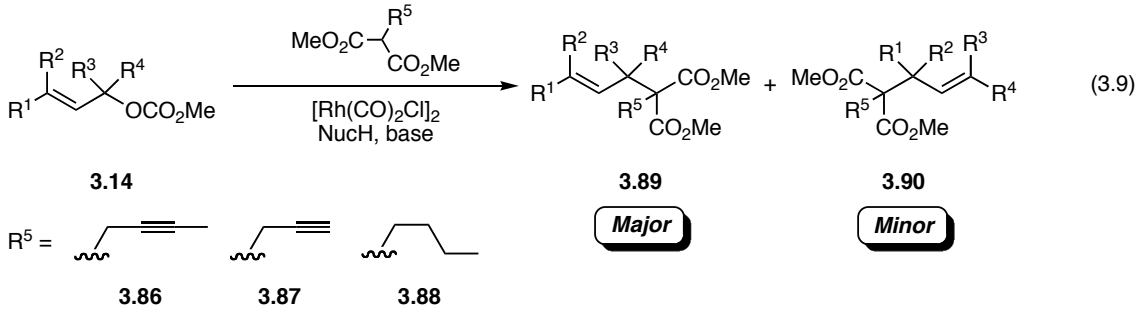
3.3 $[Rh(CO)_2Cl]_2$-CATALYZED ALLYLIC ALKYLATIONS WITH □-SUBSTITUTED MALONATES AND □-KETOESTERS

With our discovery that $[Rh(CO)_2Cl]_2$ catalyzed the direct substitution of unsymmetrical allylic carbonates with the sodium salt of dimethyl malonate in good yield and excellent regioselectivity, our focus shifted toward analyzing the scope and limitation

of the process in the context of utilizing other nucleophiles. Herein, we report an extension of this method to include alkylations involving substituted malonate derivatives and other carbon-based nucleophiles.

3.3.1 Utilizing α-Substituted Malonates as Pronucleophiles in the $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Substitution Reaction

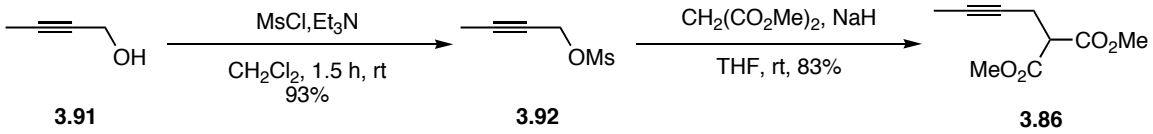
Nucleophile compatibility plays a crucial role in the expanding scope and utility of transition metal-catalyzed allylic alkylations. Previously reported catalyst systems have shown a substantial tolerance toward dialkyl malonates substituted at the α-position.[1-9] In fact, these are often the preferred nucleophiles in these types of transformations due to their softer nucleophilic character. Whereas palladium-catalyzed allylic alkylations have received the most attention in this field, analyzing the efficiency of reactions catalyzed by a rhodium(I) species has yet to be performed. To that end, the series of malonate derivatives **3.86-3.88** (Scheme 3.18) were used as nucleophiles in reaction with various unsymmetrical carbonates **3.14** in the presence of $[Rh(CO)_2Cl]_2$ to provide the substitution products **3.89** and **3.90**. The malonates **3.86-3.88** were selected because the products thus obtained could be used in subsequent reactions such as transition metal-catalyzed carbocyclizations.



(3.9)

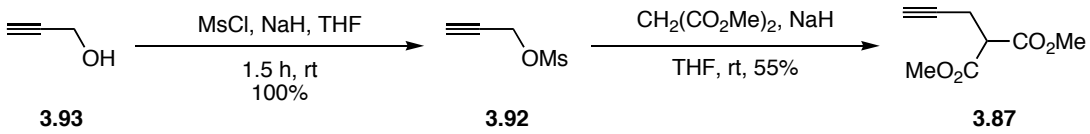
The three □-substituted malonate nucleophiles **3.86-3.88** were synthesized in a relatively straightforward manner as illustrated in Schemes 3.18 and 3.19 and Eq. 3.10. Mesylation of propargyl alcohols **3.91** and **3.93** provided the corresponding propargyl mesylates **3.92** and **3.94** in good yields. Subsequent nucleophilic displacement with sodium dimethyl malonate yielded the desired propargyl and 2-butyne substituted malonate nucleophiles **3.86** and **3.87**, respectively. The *n*-butyl substituted malonate **3.88** was prepared without incident from *n*-butyl bromide (**3.95**) and sodiodimethyl malonate.

Scheme 3.18

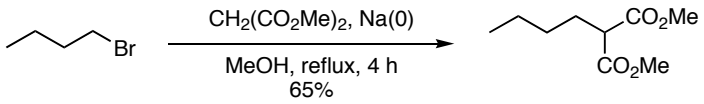


3.91 **3.92** **3.86**

Scheme 3.19



3.93 **3.92** **3.87**

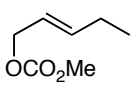
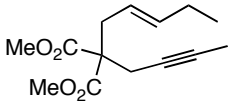
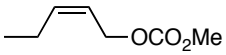
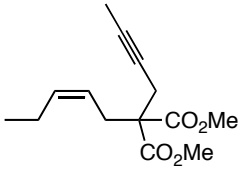
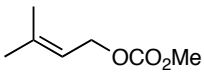
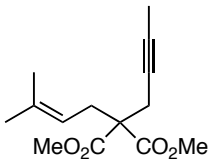
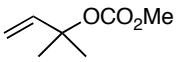
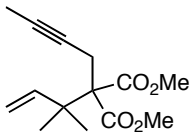
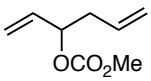
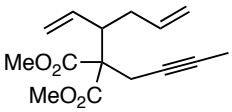
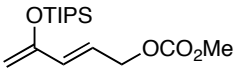
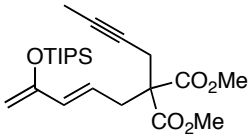


3.95 **3.88** (3.10)

With the desired malonate nucleophiles **3.86-3.88** in hand, their utility in the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation was examined with a series of carbonates. In general, good to excellent yields were obtained in all cases (Tables 3.6-3.8). It is important to note that the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations were complete in a matter of hours (1-2 h was typical) at ambient temperatures. Product distribution favored formal direct substitution as was seen in the $[Rh(CO)_2Cl]_2$-catalyzed alkylations of

unsymmetrical carbonates with sodiodimethyl malonate itself.[353] The tolerance of additional unsaturation present in the nucleophile was analyzed by examining the reactions of dimethyl 2-(but-2-ynyl)malonate (**3.86**). As illustrated by entries 1-3 in Table 3.6, the formal direct substitution products were formed preferentially from primary carbonates **3.14a**, **3.14e**, and **3.14j** in good yields. Notably, the *Z*-carbonate **3.14e** (entry 2) underwent alkylation to yield enyne **3.89b** regiospecifically and with minimal olefin isomerization under conditions analogous to those used previously (Table 3.4, entry 2). Secondary and tertiary allylic carbonates **3.14l** and **3.14m** also proved to be viable substrates in reactions with the sodium salt of malonate **3.86** to provide the corresponding products **3.89d** and **3.89e** (entries 4 and 5). Allylically transposed carbonates **3.14j** and **3.14l** furnished the corresponding substitution products **3.89c** and **3.89d** in good yields (entries 3 and 4). However, unlike the excellent regioselectivity observed when carbonate **3.14l** (99:1) was alkylated with dimethyl malonate, reaction of **3.14l** with sodiomalonate **3.86** provided **3.89d** in a diminished ratio of regioisomers (57:43) in either THF at room temperature or DMF at –20 ˚C. The reaction of carbonate **3.14m** with sodiomalonate **3.86** under identical conditions to **3.14l** also proceeded with less regiocontrol to provide **3.89e** in a 67:33 ratio. Performing the reaction in DMF at low temperatures (0 ˚C to –20 ˚C) showed no improvement in the regioselectivity. Silyl enol ether **3.14h** underwent alkylation with sodiomalonate **3.86** to provide **3.89f** with excellent regioselectivity, but in a disappointing 35% yield. Even after prolonged reaction times (>48 h), whether the alkylation was performed in THF or DMF, starting carbonate **3.14h** was still recovered from the reaction mixture.

Table 3.6. Regioselectivity in the $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation Reaction Utilizing □-Substituted Malonate **3.86**[a]

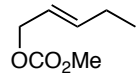
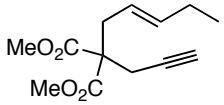
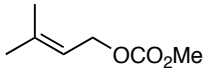
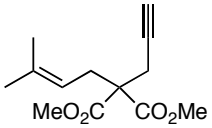
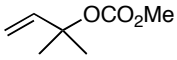
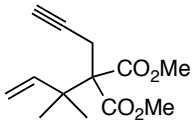
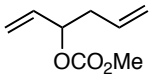
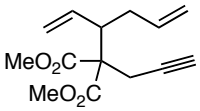
Entry	*Allylic Carbonate*	*Major Product*	*Yield (%)*[b]	*Ratio 3.89:3.90*[c]
1[d]	 **3.14a**	 **3.89a**	95	94:6
2[e]	 **3.14e**	 **3.89b**	98	100:0 (88:12)[f]
3[g]	 **3.14j**	 **3.89c**	85	99:1
4[g]	 **3.14l**	 **3.89d**	82	57:43
5[d]	 **3.14m**	 **3.89e**	74	67:33
6[d]	 **3.14h**	 **3.89f**	35	>95:5

[a]Conditions: 10 mol% $[Rh(CO)_2Cl]_2$, 1.5 equiv of malonate **3.86**, 1.4 equiv of NaH. [b]Isolated Yields. [c]Ratios determined by GLC or ^{1}H NMR (400 MHz). [d]THF, rt. [e]THF, –20 °C. [f]Ratio of cis/trans isomers. [g]DMF, –20 °C.

In some cases it has been reported that the presence of acetylenic protons has shut down carbocyclization reactions catalyzed by $[Rh(CO)_2Cl]_2$.[234] Therefore, it would be beneficial if the allylic alkylation methodology was immune to this phenomena, thereby providing the desired substitution products containing terminal carbon-carbon triple bonds. Hence, we next examined reactions of malonate **3.87** to demonstrate the feasibility of the alkylation procedure in the presence of a terminal alkyne (Table 3.7). Indeed, the reactions of carbonates **3.14a** and **3.14j** with sodiomalonate **3.87** provided the corresponding enynes **3.89g** and **3.89h** in excellent yield and regioselectivity (entries 1 and 2). Interestingly, substrate **3.14l** gave the desired enyne **3.89i** with better regiocontrol than previously observed with malonate **3.86** (entry 3). It is unclear at present why the use of malonate **3.87** should lead to a significant increase in regioselectivity for the alkylation of carbonate **3.14l**. When carbonate **3.14m** was treated with malonate **3.87**, the reaction proceeded with poor regiocontrol (entry 4) even in DMF at –20 ˚C.

In summary, the presence of a terminal acetylene seemed to exhibit no adverse effect when most allylic carbonates were subjected to the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation conditions. In at least one case, improved regiocontrol was observed than what was experienced while examining the corresponding internal alkyne. However, another yielded little to no regiocontrol. At this stage we cannot venture an explanation for these particular results.

Table 3.7. Regioselectivity in the $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation Reaction Utilizing □-Substituted Malonate **3.87**[a]

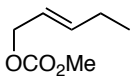
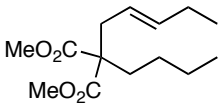
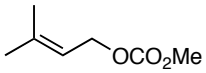
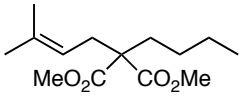
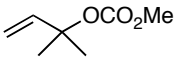
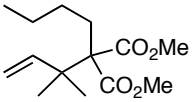
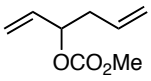
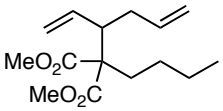
Entry	*Allylic Carbonate*	*Major Product*	*Yield (%)*[b]	*Ratio 3.89/3.90*[c]
1[d]	 **3.14a**	 **3.89g**	75	98:2
2[e]	 **3.14j**	 **3.89h**	70	99:1
3[e]	 **3.14l**	 **3.89i**	98	88:12
4[d]	 **3.14m**	 **3.89j**	71	50:50

[a]Conditions: 10 mol% $[Rh(CO)_2Cl]_2$, 1.5 equiv of malonate **3.87**, 1.4 equiv of NaH. [b]Isolated Yields. [c]Ratios determined by GLC or ^{1}H NMR (400 MHz). [d]THF, rt. [e]DMF, –20 °C.

The *n*-butyl substituted malonate **3.88** was examined to probe the effect an alkyl substitution in the nucleophile would have on the regiochemical outcome of reactions with carbonates **3.14a**, **3.14j**, **3.14l**, and **3.14m**. In each case, substitution products **3.89k-n** were formed in good to excellent yields (Table 3.8, entries 1-4). The substitution product **3.89k** was formed with excellent regioselectivity (entry 1). Interestingly enough, allylically transposed carbonates **3.14j** and **3.14l** provided the corresponding substitution products **3.89l** and **3.89m** with excellent regioselectivity (entries 2 and 3). The formation of alkylation product **3.89m** in a ratio of 93:7 shows another marked

improvement in selectivity involving substituted malonates. Finally, the reaction of allylic carbonate **3.14m** with **3.88** proceeded to yield the corresponding substitution products **3.89n** and **3.90n** as a mixture (1:1) of regioisomers in good yield (entry 4). Running the reaction in DMF at low temperatures (0 ˚C to –20 ˚C) failed to improve the regioselectivity. In general, these results seem to indicate that the absence of a coordinative functional group within the framework of substituted malonate nucleophiles does not adversely effect the direct regiochemical trends in the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation reactions.

Table 3.8. Regioselectivity in the $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation Reaction Utilizing □-Substituted Malonate **3.88**[a]

Entry	*Allylic Carbonate*	*Major Product*	*Yield (%)*[b]	*Ratio 3.89/3.90*[c]
1[d]	 **3.14a**	 **3.89k**	91	91:9
2[e]	 **3.14j**	 **3.89l**	88	99:1
3[e]	 **3.14l**	 **3.89m**	62	93:7
4[d]	 **3.14m**	 **3.89n**	71	50:50

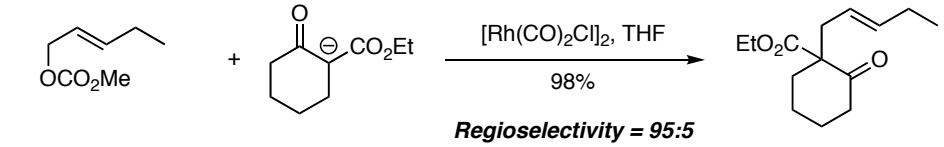
[a]Conditions: 10 mol% $[Rh(CO)_2Cl]_2$, 1.5 equiv of malonate **3.88**, 1.4 equiv of NaH. [b]Isolated Yields. [c]Ratios determined by GLC or ^{1}H NMR (400 MHz). [d]THF, rt. [e]DMF, –20 ˚C.

Examination of Tables 3.6-3.8 yields a noteworthy trend. As carbonate **3.14l** was treated with an internal alkyne, as in malonate **3.86**, the terminal acetylene **3.87**, and finally the simple butyl-substituted malonate **3.88**, formation of vicinal quaternary carbon centers did not seem to affect the chemical yield (good to excellent in each case), but the regioselectivity improved from nearly 1:1 to 13:1 in favor of the formal direct substitution product **3.89**. The fact that carbonate **3.14j** underwent *any* alkylation is noteworthy because 2,3,3-trisubstituted allylic carbonates are inert to modified Wilkinson's catalyst and typically require forcing conditions with most other transition metal catalysts.[106,277,358] In conclusion, the ability to perform the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation reaction with unsaturated, □-substituted malonates such as **3.86** and **3.87** should prove critical as the substitution products **3.89a-i** are 1,6-enynes, which can be further used in transition metal-catalyzed carbocyclization reactions to construct complex natural products.

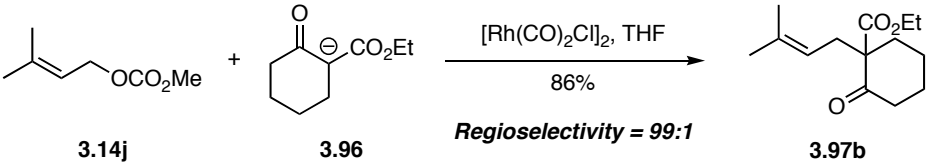
3.3.2 Utilizing □-Ketoesters as Pronucleophiles in the $[Rh(CO)_2Cl]_2$-catalyzed Allylic Substitution Reaction

□-Ketoesters were also examined as pronucleophiles in the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation in order to define the scope of this new methodology. Utilizing □-ketoesters in allylic alkylations adds another functional moiety to the chemists toolbox of available nucleophiles that can be employed in this class of transformations. Ester hydrolysis followed by decarboxylation of the □-ketoester product then yields a simple ketone that can provide an entry into various synthetically useful compounds. Ethyl 2-cyclohexanone carboxylate (**3.96**) was chosen as a representative □-ketoester.

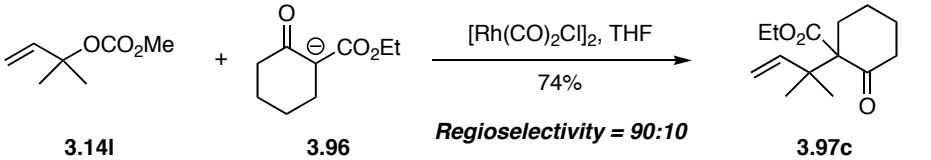
When allylic carbonate **3.14a** was treated with the sodium enolate of **3.96** in the presence of $[Rh(CO)_2Cl]_2$, **3.97a** was obtained in 98% yield and with 95:5 regioselectivity (Eq. 3.11). This result is consistent with the excellent yields and regiocontrol observed with this class of allylic carbonates regardless of the nucleophile employed. Likewise, when allylically transposed carbonates **3.14j** and **3.14l** were alkylated with the sodium enolate of **3.96** under identical conditions, the corresponding substitution products **3.97b** and **3.97c** respectively were obtained. Compound **3.97b** was isolated in 86% yield and 99:1 regioselectivity (Eq. 3.12), whereas ester **3.97c** was formed in good yield (74%) as a mixture (90:10) of regioisomers (Eq. 3.13). Of particular note is that this allylic alkylation reaction provided **3.97c**, which contains two contiguous quaternary carbon centers. The regioselectivity observed in this case is consistent with that observed for the alkylations of **3.14l** with □-substituted malonates (entry 2, Tables 3.6-3.8). The reactions exemplified by Eqs. 3.11-3.13 illustrate how □-ketoesters are useful as nucleophiles in the $[Rh(CO)_2Cl]_2$-catalyzed allylic substitution reaction, thereby increasing the scope and utility of this transformation.



3.14a **3.96** **3.97a** (3.11)



3.14j **3.96** **3.97b** (3.12)



3.14l **3.96** **3.97c** (3.13)

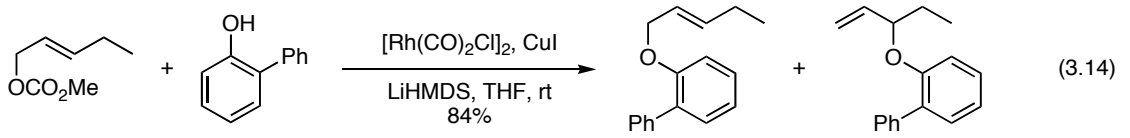
The results thus far described illustrate an efficient and reliable method in which sodium salts of substituted malonates and β-ketoesters can be used as nucleophiles in the regioselective $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation of unsymmetrical carbonates. It is noteworthy that two contiguous carbon centers can be formed. The use of substituted malonates has already been applied in the development of domino applications in which the resulting 1,6-enynes undergo an additional $[Rh(CO)_2Cl]_2$-catalyzed carbocyclization *vida infra*. Future studies may include expanding the types of carbocyclizations that can be involved, as well as their applications toward total synthesis.

3.4 HETEROATOM NUCLEOPHILES

Heteroatom nucleophiles have played an important role in expanding the utility of transition metal-catalyzed allylic alkylations in recent decades. By employing a nucleophile that incorporates either a nitrogen, oxygen or sulfur atom as the reacting center, the breadth of the reaction is increased so that the products now incorporate a heteroatom thereby making them attractive synthetic intermediates in the synthesis of complex natural products. A number of different transition metals such as palladium, molybdenum and rhodium have been used to catalyze allylic etherifications[368] and aminations[48,50,53,369,370] *en route* to polyoxygenated and alkaloid natural products. Recent reports have illustrated that sulfides can react as nucleophiles in transition metal-catalyzed alkylations. We thus decided to take a preliminary look at utilizing oxygen- and nitrogen-containing nucleophiles in the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation reaction.

3.3.1 $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Etherifications

The transition metal-catalyzed allylic etherification reaction has received less attention than the corresponding amination. A survey of the literature uncovered relatively few examples where a transition metal catalyst was used to mediate the desired allylic etherification.[368] Allylic etherifications have typically been investigated utilizing symmetrically substituted allylic systems or allylic systems with internal nucleophiles.[41,93,371-374] Examples of aliphatic alcohols being used as nucleophiles in the literature are few, presumably due to their poor nucleophilicity, whereas phenols and carboxylates have been found to be suitable coupling partners in transition metal-catalyzed carbon-oxygen bond formations.[46] Our goal was to determine if $[Rh(CO)_2Cl]_2$ could be used to prepare allylic ethers with good regioselectivity using alcohols and phenols. Studies were first performed to establish how the unsymmetrical carbonate **3.14a** would react under a variety of conditions with phenol **3.98** (Eq. 3.14). Preliminary studies on effecting the $[Rh(CO)_2Cl]_2$-catalyzed etherification of carbonate **3.14a** by *in situ* generation of phenoxide with LiHMDS failed to provide the allyl ether products.



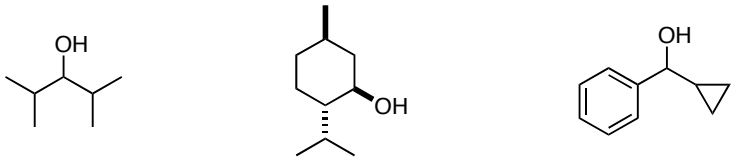
3.14a **3.98** ***4.99/4.100 = 92:8*** **3.99** **3.100** (3.14)

In 2002, Lee and coworkers reported the effectiveness of zinc(II) alkoxides as nucleophiles for the $Pd(PPh_3)_4$-catalyzed etherification of allylic acetates, to provide allyl ethers.[375] Unfortunately, treatment of carbonate **3.14a** the zinc(II) phenoxide of **3.98** generated with Et_2Zn proceeded in low yield. Evans' and coworkers reported in 2002 that treatment of unsymmetrical carbonates with copper(I) alkoxides in the presence of

$RhCl(PPh_3)_3/P(OMe)_3$ provided the products of allylic etherification.[45] The *in situ* formation of the copper(I) phenoxide obtained by sequential treatment of 2-phenyl phenol (**3.98**) with LiHMDS and CuI provided allyl ether **3.99** as a mixture (92:8) of regioisomers in 84% yield.

Although phenol **3.98** provided the best results, various other secondary alcohols were examined but failed to provide the corresponding etherification products. The secondary, rather hindered aliphatic alcohol **3.101** did not react with **3.14a** (Figure 3.2). Rather a considerable amount of the corresponding allylic alcohol was formed, presumably resulting from transesterification of the carbonate moiety. This result is not all that unusual considering that aliphatic alcohols are typically poor nucleophiles for these transformations. Additionally, when (+)-menthol (**3.102)** was chosen as an oxygen nucleophile the etherification products were not formed. Deprotonation of **3.102**, transmetallation with CuI and subsequent treatment with carbonate **3.14a** likewise failed to provide the etherification products. Instead, a complex mixture of products was obtained, none of which could be isolated cleanly from the crude reaction mixture. Cyclopropyl phenyl carbinol **3.103** also failed to provide the desired ether.

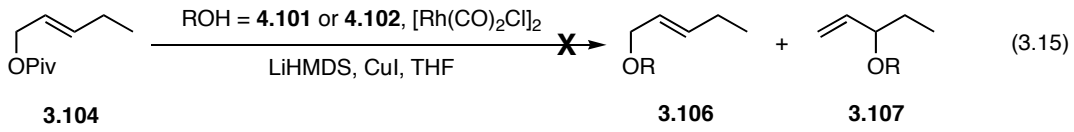
Figure 3.3. Alcohols examined in the $[Rh(CO)_2Cl]_2$-catalyzed allylic etherification reaction.



3.101 **3.102** **3.103**

Given the probability that transesterification was the dominant pathway when **3.101** and **3.102** were employed, we postulated that the reaction could be performed if a sterically crowded leaving group was used in its stead. Therefore, the methyl carbonate

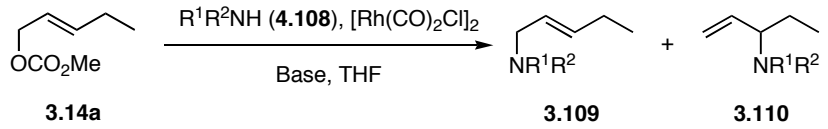
was exchanged for the sterically more crowded pivolate ester. However, treating the allylic pivolate **3.104** with the copper(I) alkoxides of **3.101** and **3.102** in the presence of $[Rh(CO)_2Cl]_2$, failed to yield the corresponding allylic etherification products **3.103c** and **3.03d** (Eq. 3.15). Future studies in examining this etherification reaction should focus on utilizing phenols with various substitution patterns, including electron withdrawing and donating substituents, and determine whether these changes affect the regioselectivities.



3.104 **3.106** **3.107** (3.15)

3.3.2 $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Aminations

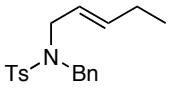
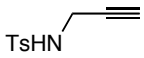
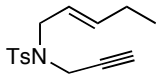
The $[Rh(CO)_2Cl]_2$-catalyzed allylic amination of unsymmetrical carbonates was also investigated. The use of transition metal-catalyzed allylic aminations for the construction of allyl amines has received increased attention from the synthetic community in recent years. The utility of these cross-coupling reactions in target-oriented synthesis is well documented.[49,51,52,376] However, the early work on transition metal-catalyzed allylic aminations primarily involved substrates that produce symmetrical π^3-metal-bound intermediates to eliminate regioselectivity issues.[48] These observations led us to examine whether $[Rh(CO)_2Cl]_2$ would catalyze the regioselective allylic amination of unsymmetrical carbonates with nitrogen nucleophiles. Thus, unsymmetrical carbonate **3.14a** was treated with various secondary nitrogen containing nucleophiles of the type **3.108** in the presence of $[Rh(CO)_2Cl]_2$ to determine the regioselectivity, and the efficiency of the transformation (Eq. 3.16).



3.14a **3.109** **3.110** (3.16)

We first examined the allylic amination of **3.14a** with a simple secondary amine. To that end, benzylmethyl amine (**3.108a**) was added to a mixture of carbonate **3.14a** and $[Rh(CO)_2Cl]_2$ in THF at room temperature (Table 3.9, entry 1). Unfortunately, we were unable to isolate either of the aminated regioisomers **3.109a** or **3.110a**. We then explored the use of deprotonated sulfonamides in these reactions. Sulfonamides make particularly attractive nucleophiles due to their ability to incorporate a protected nitrogen functionality into the products. When carbonate **3.14a** was treated with the lithium amide of propargyl *p*-toluenesulfonamide **3.108b** in the presence of $[Rh(CO)_2Cl]_2$, sulfonamide **3.109b** was obtained as a mixture of regioisomers (90:10) in good yield (78%) (entry 2). It should be noted that the utilization of LiHMDS to generate the desired anion routinely provided superior yields and regioselectivity than other bases such as LDA and NaHMDS. When carbonate **3.14a** was treated with the lithium anion of *p*-toluenesulfonamide **3.108c** in the presence of $[Rh(CO)_2Cl]_2$, allyl amine **3.109c** was obtained in moderate yield (42%) and good regioselectivity (88:12) (entry 3).

Table 3.9. Regioselectivity in the $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Amination of Carbonate **3.14a**[a]

Entry	*R^1R^2NH (3.108)*	*Major Product*	*Yield (%)[b]*	*Ratio 3.109:3.110[c]*
1[d]	MeNHBn **3.108a**	 **3.109a**	NR	–
2[e]	TsNHBn **3.108b**	 **3.109b**	78	90:10
3[f]	 **3.108c**	 **3.109c**	42	88:12

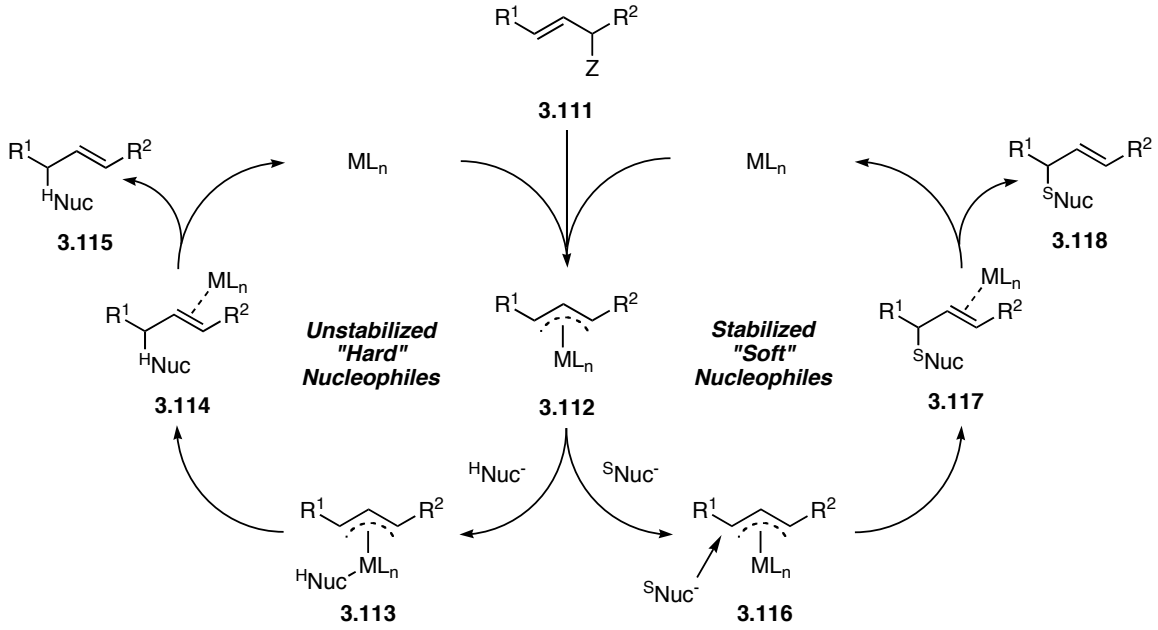
[a]Conditions: 10 mol% $[Rh(CO)_2Cl]_2$, 2.0 equiv of **3.108**, 1.9 equiv of a 1.0 M solution of LiHMDS in THF, 0.1 M in THF, room temperature. [b]Isolated Yields. [c]Ratios determined by GLC.

In conclusion, we have described preliminary results that establish limited feasibility in which phenoxides and sulfonamides can be used as nucleophiles in the regioselective $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation of unsymmetrical carbonates to give allyl ethers and allyl amines. The method described herein potentially expands the field of transition metal-catalyzed allylic substitution reactions by providing a catalyst that efficiently provides substitution products regioselectively. Future studies in this area should focus on examining various other primary and secondary unsymmetrical allylic carbonates to analyze the scope of the etherification and amination reactions. Extensions of the present methodology with regards to applications toward the synthesis of biologically active natural products, as well as the development of tandem transition metal-catalyzed processes are presently underway.

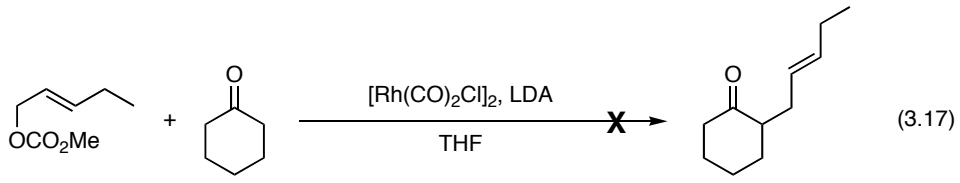
3.5 UTILIZING HARD NUCLEOPHILES IN $[Rh(CO)_2Cl]_2$-CATALYZED ALLYLIC ALKYLATIONS

It has been well established that transition metal catalysts can promote allylic alkylations in good yields with stabilized or soft nucleophiles, although unstabilized or hard nucleophiles have shown utility in the process.[28,33,72,108,115,377,378] As is illustrated in Scheme 3.20, the mechanism for this class of reactions is thought to be slightly different than that for stabilized anions. Namely, when hard nucleophiles (^{H}Nuc) are used, transmetallation is believed to occur to place the anion on the transition metal-stabilized η^3-allyl complex **3.112** to form complex **3.113**. Migratory insertion of ^{H}Nuc to the η^3-allyl moiety forms the carbon-carbon bond present in **3.114**, and decomplexation of the transition metal yields the substitution product **3.115**. Alternatively, soft nucleophiles (^{S}Nuc) react intermolecularly to form the carbon-carbon bond as illustrated by complex **3.116**. Subsequent decomplexation of the catalyst provides the product **3.118**.

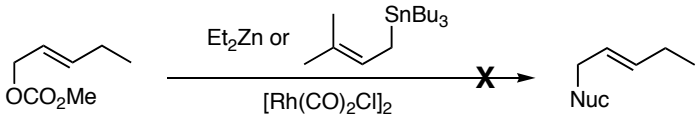
Scheme 3.20



In an effort to expand the array of nucleophiles that can be used, we examined the reaction of carbonate **3.14a** with various "hard" nucleophiles. However, treatment of carbonate **3.14a** with the lithium enolate of cyclohexanone (**3.119**) in the presence of $[Rh(CO)_2Cl]_2$ failed to provide either of the two regioisomeric substitution products (Eq. 3.14). Likewise, when carbonate **3.5a** was treated with either diethyl zinc or isopropenyl tributyltin, the expected coupling product **3.118** was not observed. These preliminary results seem to indicate that hard anions are not compatible with $[Rh(CO)_2Cl]_2$ as allylic alkylation substrates. However, the potential for enabling this reaction still exists in that future experiments may include the use of more easily ionizable allylic substrates, different metal cations (*i.e.* copper(I) enolates) for enolate alkylations, and organometal reagents derived from sp^2 or sp^3 organic starting materials.



3.14a **3.119** **3.120** (3.17)



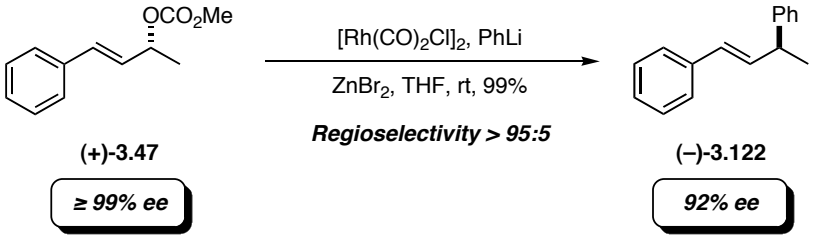
3.14a **3.121** (3.18)

Nuc = Et, isopropenyl

As described in Chapter 1, Evans illustrated the use of arylzinc halides, generated *in situ* from $ZnBr_2$ and an aryl lithium reagent, to arylate allylic fluorinated carbonates in the presence of $TpRh(C_2H_4)_2$, LiBr and dibenzylidene acetone (dba) regioselectively with overall net inversion of configuration. However, this process suffers from the need to use

an extremely labile leaving group, a rhodium source that is not commercially available, and a mixture of reagents that renders the overall process very inefficient from an atom economical standpoint.

With this as precedent, we wondered whether this reaction could be simplified by using a standard allylic methyl carbonate substrate, and an arylzinc halide in the presence of $[Rh(CO)_2Cl]_2$ without the need to supplement the reaction mixture with LiBr or additional ligands. Gratifyingly, when enantioenriched carbonate **(+)-3.47** was treated with phenylzinc bromide in the presence of $[Rh(CO)_2Cl]_2$ at room temperature, the arylated product **(–)-3.122** was obtained in less than 15 minutes in excellent yield and regioselectivity with net *inversion* of absolute configuration (Eq. 3.19). Chiral HPLC analysis of **(–)-3.122** showed that the reaction proceeded with minimal loss of enantiopurity, and comparison of the optical rotation to literature values confirmed the absolute stereochemical configuration in the product. Future studies should focus on examining the scope of this process, whether the arylation proceeds stereoselectively and if the product is obtained with net inversion or retention of configuration.



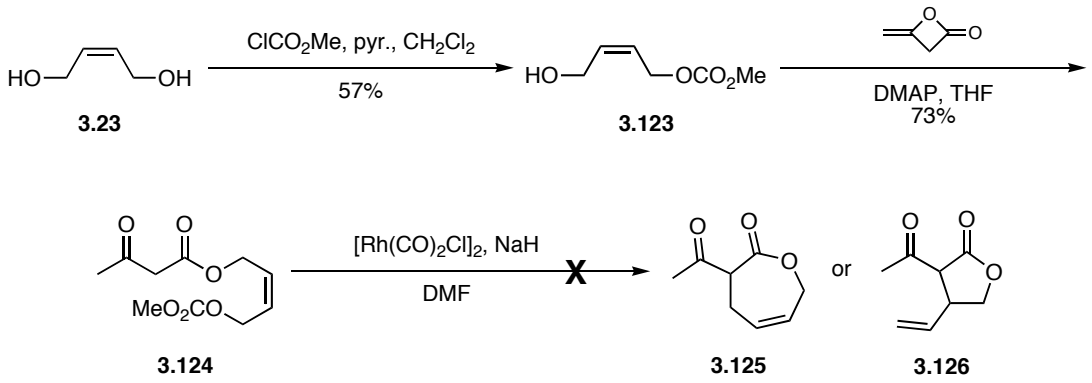
(3.19)

3.6 INTRAMOLECULAR $[Rh(CO)_2Cl]_2$-CATALYZED ALLYLIC ALKYLATIONS FOR THE SYNTHESIS OF MEDIUM-SIZED RINGS

We have thus demonstrated that $[Rh(CO)_2Cl]_2$ has the propensity to catalyze allylic substitutions of unsymmetrical substrates at the carbon atom bearing the leaving group. The obvious question that now arises is: How can this unusual reactivity be exploited in synthesis? The allylic substitutions of *Z*-alkenes proceeding with retention of double bond geometry suggest that this methodology could be used in an intramolecular sense to form medium and large rings containing *Z*-olefins. Transition metal-catalyzed cyclizations to synthesize rings has received considerable attention since the early 1980's.[62-64] Inasmuch as the synthesis of seven-membered rings is particularly demanding, we first examined whether seven-membered lactones might be formed by $[Rh(CO)_2Cl]_2$-catalyzed cyclizations.

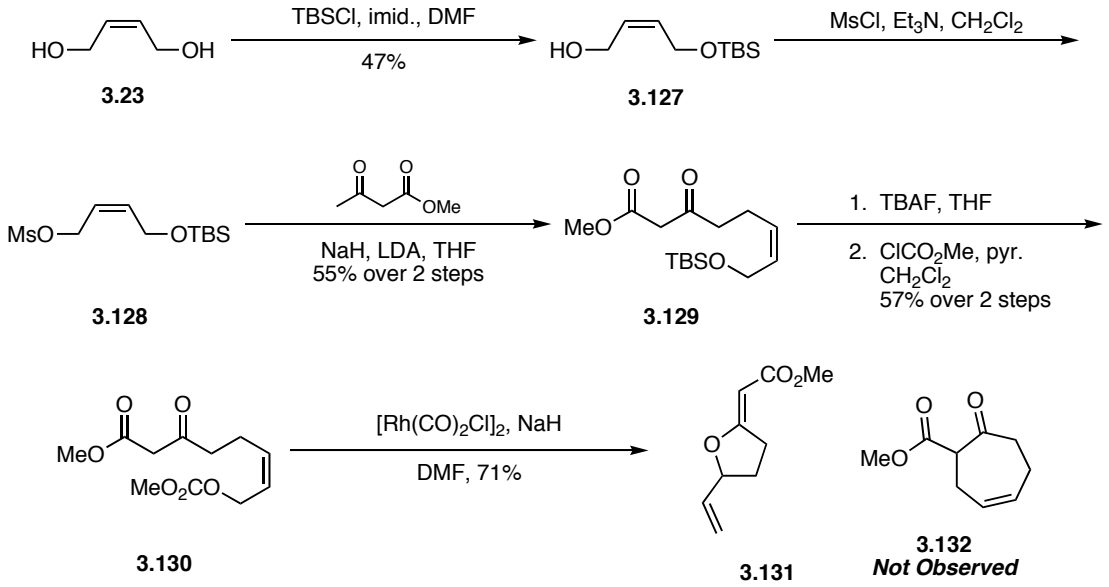
Toward this end, we first targeted **3.124**, which was synthesized in two steps from commercially available *cis*-2-buten-1,4-diol (**3.23**) (Scheme 3.21). Monoacylation of diol **3.23** with methyl chloroformate and pyridine provided monocarbonate **3.123** in 57% yield. Subsequent acylation of alcohol **3.123** with diketene in the presence of DMAP yielded acetoacetate **3.124** in 73% yield. Unfortunately, treatment of carbonate **3.124** with NaH and then $[Rh(CO)_2Cl]_2$ failed to yield either the desired 7-membered lactone **3.125** or the 5-membered analogue **3.126**. A potential complication with the desired cyclization may arise in part because of the allylic nature of the β-ketoester functionality. This may lead to competitive π^3-allyl intermediates, which would fail to produce the desired alkylation products. However, as no identifiable products were obtained from the reaction mixture, this hypothesis is purely conjecture at this point.

Scheme 3.21



To avoid any potential complications with a bisallylic substrate, we turned toward synthesizing the cyclic ketone **3.132**, the carbocyclic analog of lactone **3.125** (Scheme 3.22). Toward that end, **3.130** was prepared in five steps from diol **3.23**. Monosilylation of diol **3.23** with TBSCl in the presence of imidazole provided alcohol **3.127** in 47% yield. Mesylation of the remaining primary alcohol provided mesylate **3.128**, which was immediately alkylated with the dianion of methyl acetoacetate to provide acetoacetate **3.129** in 55% yield over two steps. The silyl group was removed with TBAF, and the resulting alcohol was converted under standard conditions to give carbonate **3.130**. Sequential treatment of -ketoester **3.130** with NaH then $[Rh(CO)_2Cl]_2$ in DMF at room temperature provided the O-alkylation product **3.131** with none of the corresponding seven-membered carbocycle **3.132** was observed.

Scheme 3.22



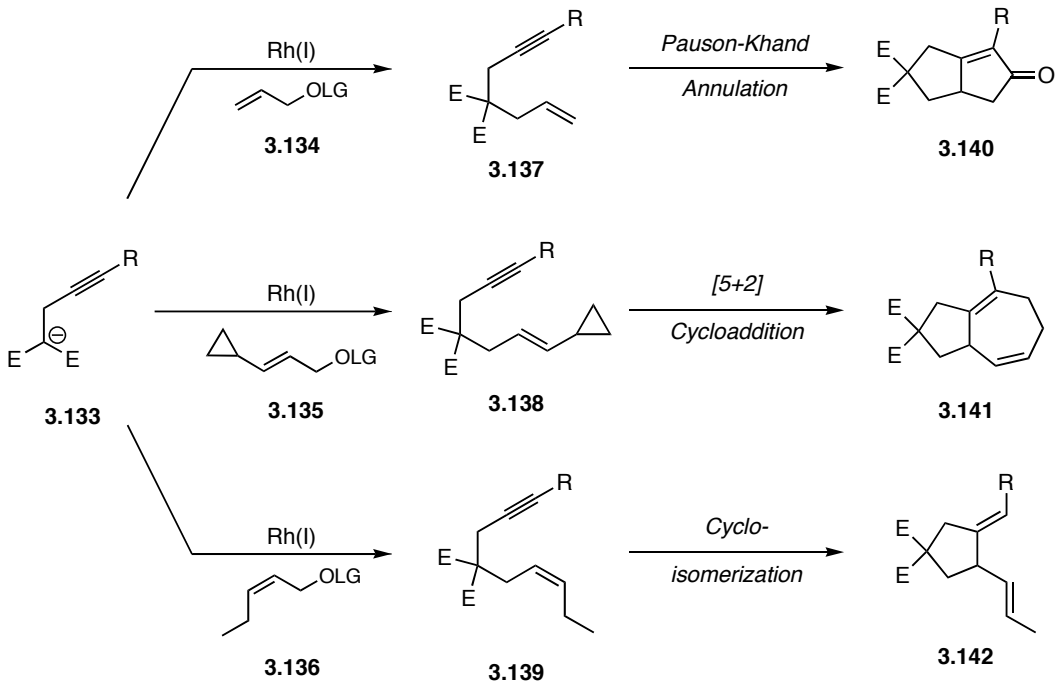
3.7 APPLICATIONS TO DOMINO PROCESSES

Recently there has been a major push toward developing synthetic methods to transform relatively simple starting materials into structurally complex intermediates with high efficiency and atom economy. One way in which this can be accomplished is to execute sequential reactions wherein the product of the first serves as the starting material for the second and where *each* transformation is catalyzed by the *same* transition metal. Such processes enable the preparation of desired targets with minimal expenditure of raw materials, energy, and waste. One goal of modern-day organometallic exploration has been the development of multifunctional catalysts that can be utilized to promote mechanistically discrete domino reactions.[288] Although, the transition metal-catalyzed allylic alkylation has been widely studied,[5,12,13] the utility of this reaction has been significantly expanded by the development of domino reaction processes in which the

allylic substitution serves as the initial construction.[291,379] We now report several novel domino reactions that are catalyzed by $[Rh(CO)_2Cl]_2$.

Our attention on domino reactions began shortly after our initial discovery that $[Rh(CO)_2Cl]_2$ catalyzed highly regio- and stereoselective allylic alkylations to provide products arising from substitution at the carbon atom bearing the leaving group, irrespective of the structure of the starting carbonate.[353] The significance of this discovery became ever more apparent as we realized to what extent $[Rh(CO)_2Cl]_2$ and other rhodium(I) catalysts catalyzed a number of carbocyclization reactions, including intramolecular variants of the Pauson-Khand reaction (PKR),[127,267,380] [5+2] cycloadditions,[236,239,337] and cycloisomerizations of 1,6-enynes.[134,267,284] In order to expand the utility of our rhodium(I)-catalyzed allylic alkylation method, we set to the task of developing $[Rh(CO)_2Cl]_2$ as a multifunctional catalyst to promote various domino reactions. These reactions could then be exploited to assemble complex molecular architectures of the general types **3.140-3.142** from simple starting materials **3.137-3.139** according to the general strategy set forth in Scheme 3.23.

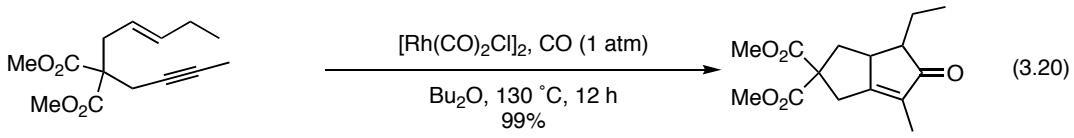
Scheme 3.23



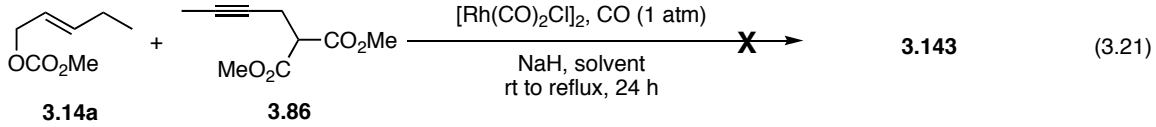
3.7.1 Development of the Domino $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation/Pauson-Khand Annulation

As noted in Chapter 1, Evans' reported in 2001 that $[RhCl(CO)dppp]_2$ was capable of catalyzing a regio- and diastereoselective tandem allylic alkylation/Pauson-Khand annulation of simple carbonates with appropriately functionalized carbon and nitrogen nucleophiles.[291] We were thus encouraged to determine whether $[Rh(CO)_2Cl]_2$ was capable of catalyzing a similar transformation. That such a process should be feasible was suggested by the fact that $[Rh(CO)_2Cl]_2$ was known to catalyze efficiently the Pauson-Khand reaction for a variety of enynes (see Chapter 1). In order to ascertain whether this catalyst would promote a PKR of a substrate that might be produced by the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation, the enyne **3.89a** was treated with $[Rh(CO)_2Cl]_2$

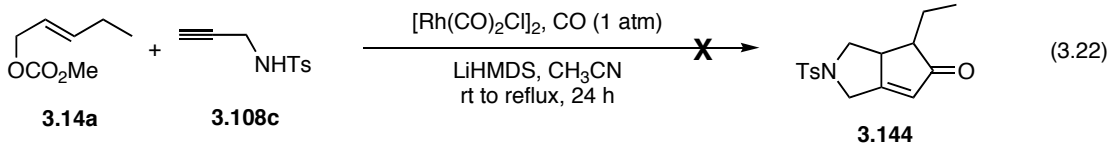
under an atmosphere of CO in Bu_2O at 130 ˚C for 12 h to provide the desired [3.3.0] bicycle **3.143** in 99% yield (Eq. 3.20).[260] However, when allylic carbonate **3.14a** was alkylated with 1.2 equivalents of sodiomalonate **3.86** in the presence of $[Rh(CO)_2Cl]_2$ under a blanket of CO (1 atm) in a variety of solvents, good conversion to enyne **3.89a** was observed by TLC, but no PKR product was obtained (Eq. 3.21). Allylic amination of carbonate **3.14a** with 1.2 equivalents of sulfonamide **3.108c** and subsequent heating of enyne **3.109c** under an atmosphere of CO also failed to provide the desired [3.3.0] bicycle **3.144** (3.22).



3.89c **3.143** (3.20)



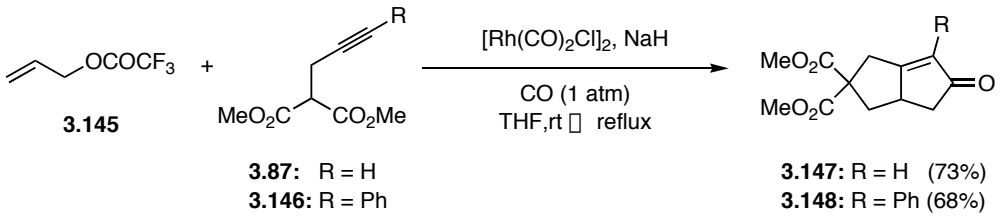
3.14a **3.86** **3.143** (3.21)



3.14a **3.108c** **3.144** (3.22)

Not completely disheartened by the lack of positive results, there still existed a variety of reaction parameters that needed to be analyzed before achieving the desired domino allylic alkylation/Pauson-Khand reaction would be abandoned. Having thus established that $[Rh(CO)_2Cl]_2$ catalyzed alkylations of □-substituted malonates with allylic carbonates, we turned our attention toward developing the desired domino allylic alkylation/carbocyclization reactions by first determining whether it was the allylic

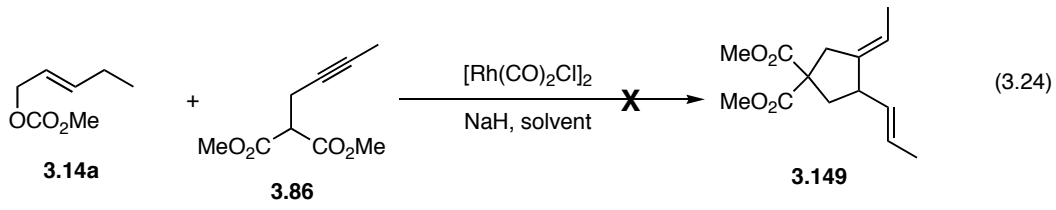
alkylation or the PKR that inhibited the domino process. Although allylic carbonates and acetates may be used as substrates in the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations, poor yields were seen when these traditional substrates were employed for the domino reaction sequence. However, after considerable experimentation, a graduate student in our group, Kenneth A. Miller discovered that when allylic trifluoroacetates were used as substrates the domino process proceeded in good yield. Thus, Miller showed that allyl trifluoroacetate **3.145** reacted smoothly with the anion of malonates **3.87** and **3.146** in the presence of $[Rh(CO)_2Cl]_2$ (10 mol%) under an atmosphere of CO to yield bicyclic enones **3.147** and **3.148** in good overall yields (Eq. 3.23). After optimization, Miller showed that the allylic substitution reaction proceeded rapidly at room temperature, whereas the subsequent PKR required heating under reflux to push the reaction to completion (12–24 h). To date this scope of this reaction seems limited by the requirement that the allylic substrate be **3.145**. Unsymmetrically substituted allylic trifluoroacetates have thus far failed to yield the desired bicyclic enones under identical conditions. Further studies to apply this reaction to form the heterobicyclic enone **3.144** and related intermediates are in progress.



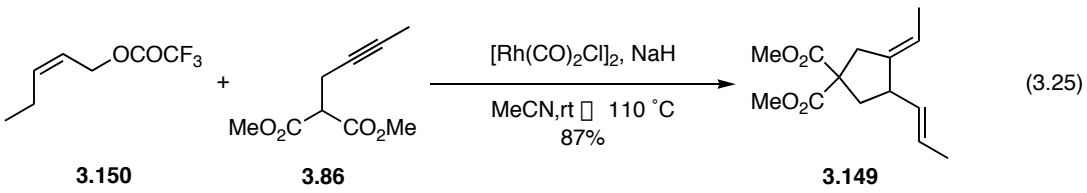
(3.23)

3.7.2 Development of the $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation/Cycloisomerization Reaction

During the course of our studies we discovered somewhat surprisingly that $[Rh(CO)_2Cl]_2$ catalyzed the facile isomerization of enynes to yield vinyl alkylidene cyclopentanes. The cyclization of 1,6-enynes leading to the formation of 1,4-dienes is an excellent example of a synthetic strategy that is challenging or nearly impossible to perform without the use of a transition metal catalyst. Although cationic rhodium(I) catalysts are well known to promote such reactions,[134,284] neutral rhodium(I) catalysts have not been reported to catalyze this class of carbocyclizations. Initial efforts involving the reaction of carbonate **3.14a** with malonate **3.86** failed to produce the desired 1,4-diene **3.149** (Eq. 3.24). Heating the reaction for extended reaction times at reflux following initial formation of the intermediate enyne **3.89a** resulted in unidentifiable side products. Fortunately, a graduate student in our group, Anna J. Smith, discovered that when allylic trifluoroacetate **3.150** was treated with the anion of malonate **3.86** at room temperature in the presence of $[Rh(CO)_2Cl]_2$, the intermediate enyne arising from the regioselective allylic alkylation underwent cycloisomerization upon heating to provide **3.149** (Eq. 3.25).



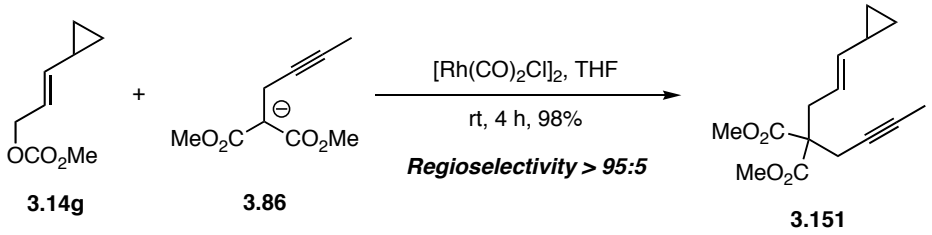
(3.24)



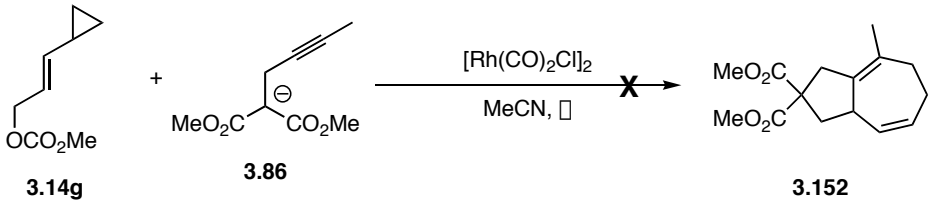
(3.25)

3.7.3 A Novel $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation/Intramolecular [5+2] Cycloaddition

We next investigated the tandem $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation/[5+2] cycloaddition that initially led us to the discovery that $[Rh(CO)_2Cl]_2$ catalyzed the allylic alkylation reaction to begin with. Before we examined the tandem process, it was necessary to establish the feasibility of the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation of an allylic carbonate containing a vinyl cyclopropane moiety. To that end, carbonate **3.14g** was treated with the anion of malonate **3.86** to provide cyclopropyl enyne **3.151** in excellent yield (98%) and regioselectivity (>95:5) (Eq. 3.26). Although the allylic substitution reaction proceeded at room temperature, standard conditions for rhodium(I)-catalyzed [5+2] cycloadditions require elevated temperatures (typically 110 ˚C in PhMe). Therefore, initial attempts at effecting the domino process focused on using higher boiling solvents. However, when the domino sequence was attempted with carbonate **3.14g** and malonate **3.86** in MeCN, none of the desired cycloadduct **3.152** was formed; only enyne **3.151** was observed (3.27).

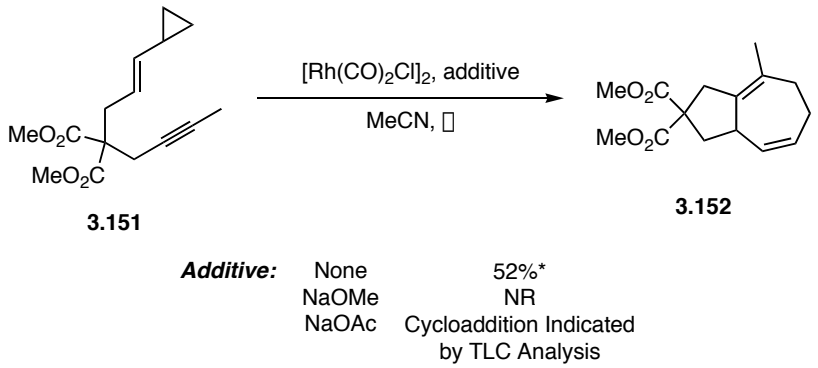


(3.26)



(3.27)

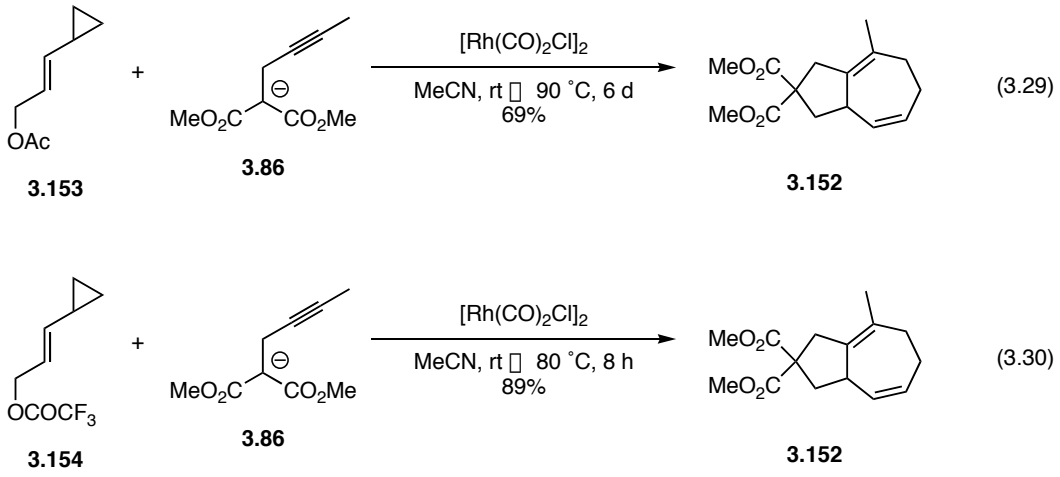
Suspecting that the methyl carbonate leaving group, which has been proposed to decarboxylate upon ionization in allylic alkylations to form CO_2 and MeO^-, was hindering the subsequent [5+2] cycloaddition, we examined the cycloaddition of enyne **3.151** in the presence of the sodium salts which would be produced from allylic substrates. In model studies performed by a talented undergraduate student, Kristy Tran, enyne **3.151** was heated in the presence of $[Rh(CO)_2Cl]_2$ to give cycloadduct **3.152** in an unoptimized 52% (Eq. 3.28). When the cycloaddition was performed in the presence of NaOMe, only the starting enyne **3.151** was obtained from the reaction mixture. However, when NaOAc was added to a solution of enyne **3.151** and $[Rh(CO)_2Cl]_2$, the cycloadduct **3.152** was formed as indicated by TLC. This result led us to examine allylic acetates as substrates in the domino sequence.



(3.28)

Allylic acetate **3.153** was treated with the sodiomalonate **3.86** in the presence of $[Rh(CO)_2Cl]_2$ under a variety of conditions in attempts to obtain cycloadduct **3.152**. Kristy Trans screened a number of solvents and temperatures including THF at 110 ˚C (bath temperature in a sealed vial), PhMe from 90-110 ˚C, DMF from 110-150 ˚C and MeCN from 90-110 ˚C (bath temperature in a sealed vial) in attempts to optimize the domino sequence. She found that the best results were obtained when the reaction was

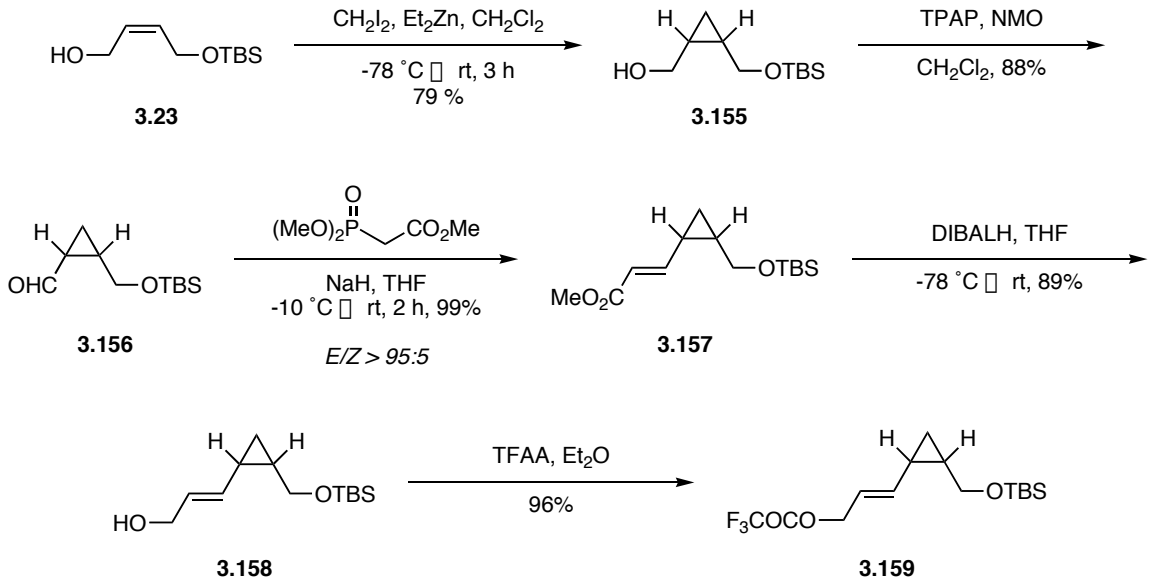
allowed to run over the course of six days thereby providing cycloadduct **3.152** in 69% yield (Eq. 3.29). In these experiments, we found that there existed a delicate balance between time and temperature. Elevated temperatures for extended periods of time often resulted in low yield, presumably due to decomposition of either enyne **3.151** or cycloadduct **3.152** as indicated an increase in material remaining at the baseline in the TLC. However, if the reaction was stopped too early, insufficient conversion to product was observed, yielding primarily enyne **3.151** and recovered allylic acetate **3.153**. Optimal conditions would allow for the allylic alkylation to proceed rapidly at room temperature, whereupon the reaction would be heated to promote the [5+2] cycloaddition before decomposition can occur. Because the substitution reaction was often not going to completion, a more reactive acetate derivative was examined. In the end, allylic trifluoroacetate **3.154** was treated with sodiomalonate **3.86** in the presence of $[Rh(CO)_2Cl]_2$ at room temperature, and then the mixture was warmed to 80 ˚C (bath temperature) to provide cycloadduct **3.152** in 89% yield after 8 h (Eq. 3.30).



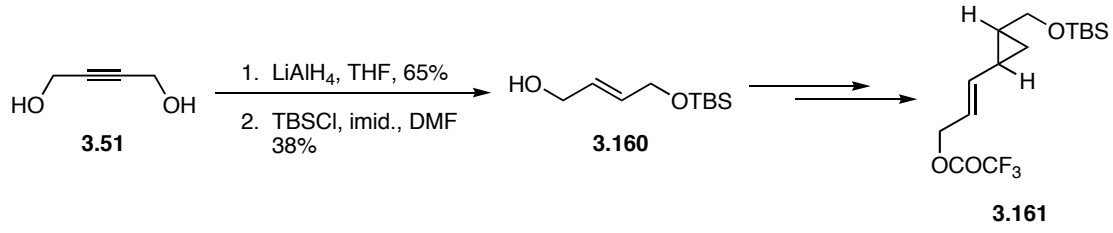
Having established optimized conditions, our next goal was to determine whether the domino allylic alkylation/[5+2] cycloaddition would proceed with the same regio-

and diastereoselectivity Wender observed in the [5+2] cycloaddition of various cyclopropyl enynes. Thus, *cis*- and *trans*- substituted cyclopropane allylic trifluoroacetates **3.159** and **3.161** respectively were targeted as substrates for a domino $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation/[5+2] cycloaddition reaction. Trifluoroacetate **3.159** was obtained as illustrated in Scheme 3.24 from alcohol **3.23**. Simmons-Smith cyclopropanation of alcohol **3.23** provided *cis*-cyclopropane **3.155** in very good yield (79%). Notably, if diiodomethane was not added to a solution of substrate and diethylzinc at –78 ˚C, the yield of the transformation was significantly lower (<60%). Oxidation of alcohol **3.155** proceeded uneventfully to yield aldehyde **3.156** in 88% yield. Subsequent HWE-olefination yielded the *trans*-□,□-unsaturated ester **3.157** with excellent control of olefin geometry (>95:5) in 99% yield. Reduction of **3.157** with DIBALH provided allylic alcohol **3.158**, which upon treatment with trifluoroacetic anhydride in Et_2O at room temperature yielded the desired trifluoroacetate **3.159**. The corresponding *trans*-cyclopropane **3.161** was obtained in a similar sequence of synthetic steps. Namely, treatment of 2-butyn-1,4-diol (**3.51**) with $LiAlH_4$ in THF provided the *trans*-2-buten-1,4-diol, which was immediately monosilylated with TBSCl in the presence of imidazole to yield alcohol **3.160** (Scheme 3.25). Following the same route used to synthesize **3.159**, we were able to obtain trifluoroacetate **3.161** in good overall yield.

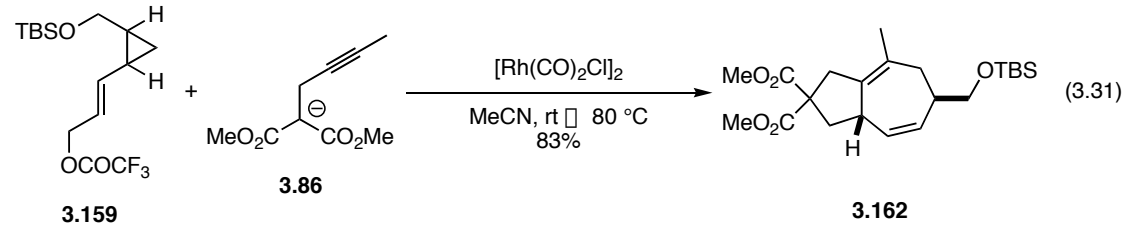
Scheme 3.24

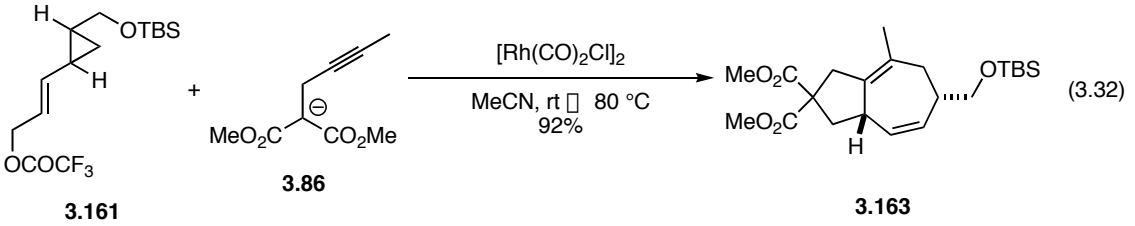


Scheme 3.25



Thus, subjecting allylic trifluoroacetates **3.159** and **3.161** were subjected to the optimized conditions to provide cycloadducts **3.162** and **3.163**, respectively, in excellent overall yields (Eqs. 3.31 and 3.32). The regiochemistry and diastereoselectivity in the *in situ* [5+2] cycloaddition proceeded in accord with precedent established by Wender. The ^{1}H NMR spectra of cycloadducts **3.162** and **3.163** were similar in all aspects to the published spectral data.[237]





In summary, we have discovered that the commercially available complex $[Rh(CO)_2Cl]_2$ catalyzes facile and efficient domino processes that feature an initial allylic alkylation followed by one of three different carbocyclizations, including the Pauson-Khand reaction, cycloisomerization, and [5+2] cycloaddition. The ability to exploit multifunctional catalysts to promote two or more sequential reactions in a single operation has significant potential for the preparation of structurally complex targets from simple starting materials. These results suggest that $[Rh(CO)_2Cl]_2$ serves as a highly effective, multifunctional catalyst that can promote a variety of mechanistically different reactions in a single operation. Studies to explore these and other $[Rh(CO)_2Cl]_2$-catalyzed cascade reactions are in progress.

3.8 CONCLUSIONS

Although there is no disputing the wealth of knowledge that exists on the subject of transition metal-catalyzed allylic alkylations, there remains a great deal yet to be learned about this often-utilized transformation. The issue of regiocontrol in these

reactions is typically of primary importance. Different catalyst systems have subsequently been developed to control all possible regiochemical outcomes one might expect from nucleophilic addition to a metal stabilized allyl complex. The seminal work by a number of research groups has focused on controlling such regioselectivity through the use of steric or electronic constraints put in place by the construction of a suitable substrate. However, in recent years the focus has shifted from controlling the regioselectivity by utilizing an appropriately substituted allylic substrate, toward directing the outcome by varying the electronic nature of the catalyst.

Throughout the years chemists have been capable of manipulating the regioselectivity in transition metal-catalyzed allylic alkylations to provide allylic substitution products derived from alkylation at the less hindered allylic termini, as well as those that would result from nucleophilic attack at the more substituted carbon of the allylic system. However, until now, a reliable and efficient method had yet to be identified that would allow for a direct correlation between the position of the allylic leaving group and the site of nucleophilic substitution in transition metal-catalyzed allylic alkylations. With the discovery that $[Rh(CO)_2Cl]_2$ is capable of catalyzing allylic alkylations to provide product distributions regio- and stereoselectively, we feel as though a critical hole in the field of transition metal catalysis has been filled.

The use of $[Rh(CO)_2Cl]_2$ as an allylic alkylation catalyst incorporates a number of advantages that separate it from most other metals used for this transformation. First, the formal direct substitution pattern and excellent regiocontrol exhibited is unlike any observed with other catalysts. Secondly, the mild conditions with which the reaction can be performed make it useful for thermally sensitive substrates. Third, the catalyst employed is quite unusual among transition metals used for these reactions. The ligandless nature and the commercial availability of the catalyst is a salient feature of the

methodology. Additionally, the unnecessary use of stringent procedures designed for the exclusion of oxygen, and incubation times to derive the active catalyst species typically associated with a variety of allylic alkylation catalysts, add to the appeal of $[Rh(CO)_2Cl]_2$. Finally, the wide array of other transformations which $[Rh(CO)_2Cl]_2$ is capable of catalyzing makes it a prime candidate for the development of domino processes. The highly convergent and atom economical nature of the domino processes allow for the rapid assembly of complex carbocyclic intermediates from relatively simple substrates..

In summary, we have discovered that the commercially available catalyst $[Rh(CO)_2Cl]_2$ may be used to catalyze the facile allylic alkylation of unsymmetrical substrates. Because $[Rh(CO)_2Cl]_2$ is known to catalyze other transformations, a number of synthetic applications may be envisaged in which allylic alkylations are combined with other transformations, resulting in cascade processes to rapidly assemble complex structures. This concept was illustrated by development of the first domino allylic alkylation/cycloisomerization and allylic alkylation/[5+2] cycloaddition. The method was also expanded to include the domino allylic alkylation/Pauson-Khand annulation. Future experiments to elucidate the mechanistic details, scope and utility of $[Rh(CO)_2Cl]_2$-catalyzed allylic substitutions and whether chiral ligands may be employed as additives for enantioselective applications are in progress and will be reported in due course. In conclusion, this $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation method should find great utility in the field of synthetic organic chemistry as both a tool for further developing new classes of reactions as well the synthesis of complex natural, or unnatural, products.

Chapter 4. Experimental Procedures

4.1 GENERAL

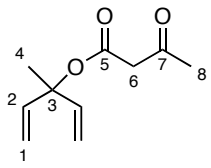
Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were filtered through two columns of neutral alumina prior to use. Acetonitrile (CH_3CN) and methanol (MeOH) were filtered through two columns of molecular sieves prior to use. *N,N*-dimethyl formamide (DMF) was filtered through two columns of molecular sieves prior to use. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), and *N,N*-dimethylaniline were distilled from calcium hydride prior to use. Toluene was filtered through one column of neutral alumina and one column of Q5 reactant prior to use.

Air- and moisture-sensitive reactions were performed in oven-dried glassware with rubber septa under a positive pressure of dry nitrogen or argon from a manifold or balloon. Similarly air-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Reaction mixtures were stirred using Teflon-coated stir bars. Elevated temperatures were maintained using Thermowatch-controlled sand or silicon oil baths. Organic solutions were concentrated using a Büchi rotary evaporator with a Büchi digitally controlled diaphragm pump. Flash column chromatography was performed following the Still protocol[381] using EM silica gel 60 (230~400 mesh). Analytical TLC was performed using Merck-60 TLC plates. The plates were visualized either by an ultraviolet light source, or immersion in a *p*-anisaldehyde, ceric ammonium molybdate, potassium permangenate, or phosphomolybdic acid solution followed by gentle heating.

^1H and ^{13}C NMR spectra were measured on a Bruker AC-250, Varian INOVA 500, or Varian Gem-300 magnetic resonance spectrometer. Chemical shifts for ^1H and ^{13}C NMR spectra are expressed in parts per million (□) relative to tetramethylsilane with

either TMS or residual solvent as an internal reference for ^{1}H, and residual solvent for ^{13}C unless otherwise noted. The following format was used to assign chemical shift peaks: chemical shift (ppm), (multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, dt = doublet of triplets, m = multiplet, comp = multiple lines of magnetically different hydrogen atoms, app = apparent), coupling constant(s) (Hz), integration).

4.2 COMPOUNDS

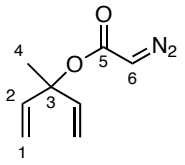


2.38

3-Methylpenta-1,4-dien-3-yl acetoacetate (2.38) (BLA-II-220). A solution of freshly distilled diketene (1.048 g, 12.5 mmol) in THF (2 mL) was added dropwise to a stirred mixture of *N,N*-dimethylaminopyridine (DMAP) (152 mg, 1.25 mmol), sodium acetate (102 mg, 1.25 mmol), and **2.37** (610 mg, 6.23 mmol) (synthesized from 2-methyl-2-vinyloxirane **2.36** and trimethylsulfonium iodide)[310] in THF (18 mL) at –10 °C. The reaction was allowed to warm to room temperature by removal of the cooling bath and stirred for 5.5 h. Saturated aqueous NaCl (20 mL) and Et_2O (20 mL) were added, and the layers were separated. The aqueous phase was extracted with Et_2O (2 x 20 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by Kugelrohr distillation (55-57 °C, 0.1 mmHg) to yield 1.052 g (93%) of **2.38** as a colorless oil: ^{1}H NMR (300 MHz) 6.08 (dd, *J* =

17.4, 10.8 Hz, 2 H), 5.20 (m, 4 H), 3.38 (s, 2 H), 2.23 (s, 3 H), 1.61 (s, 3 H); ^{13}C NMR (65 MHz) 200.7, 165.6, 139.7, 114.7, 83.3, 51.0, 30.1, 23.9; IR ($CHCl_3$) 2987, 1744, 1720, 1642, 1410, 1361, 1318, 1269, 1149, 997, 932 cm^{-1}; mass spectrum (CI) *m/z* 183.1028 [$C_{10}H_{15}O_3$ (M+1) requires 183.1021] 165, 161, 159, 139, 135, 121, 103 (base).

NMR Assignments: ^{1}H NMR (300 MHz) 6.08 (dd, *J* = 17.4, 10.8 Hz, 2 H, C2-H), 5.20 (m, 4 H, C1-H), 3.38 (s, 2 H, C6-H), 2.23 (s, 3 H, C8-H), 1.61 (s, 3 H, C4-H); ^{13}C NMR (65 MHz) 200.7 (C5), 165.6 (C7), 139.7 (C2), 114.7 (C1), 83.3 (C3), 51.0 (C6), 30.1 (C8), 23.9 (C4).

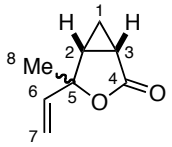


2.9

3-Methylpenta-1,4-dien-3-yl diazoacetate (2.9) (BLA-II-103). A solution of *p*-toluenesulfonyl azide (826 mg, 4.28 mmol) (synthesized from *p*-toluenesulfonyl chloride and sodium azide)[382] in CH_3CN (6 mL) was added to a stirred solution of **2.38** (648 mg, 3.57 mmol) and Et_3N (0.75 mL, 5.35 mmol) in CH_3CN (30 mL) at room temperature. The reaction was stirred for 4 h, whereupon a solution of $LiOH•H_2O$ (449 mg, 10.7 mmol) in H_2O (3.5 mL) was added, and the reaction was stirred for an additional 4 h. The mixture was diluted with water (30 mL) and extracted with Et_2O (3 x 30 mL). The combined organic fractions were washed with saturated aqueous NaCl (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (10:1) to give 573 mg (97%) of **2.9** as a yellow oil: ^{1}H NMR (300 MHz) 6.08 (dd, *J* = 17.5, 10.7 Hz, 2 H), 5.23 (d, *J* = 17.5 Hz,

2 H), 5.18 (d, *J* = 10.7 Hz, 2 H), 4.69 (br s, 1 H), 1.65 (s, 3 H); ^{13}C NMR (65 MHz) δ 171.0, 140.2, 131.8, 114.1, 82.6, 20.8; IR ($CHCl_3$) 3033, 2985, 2109, 1694, 1371, 1248, 1186, 1092, 992, 924, 740 cm^{-1}; mass spectrum (CI) *m/z* 167.0821 [$C_8H_{11}N_2O_2$ (M+1) requires 167.0821] 166 (base), 143, 142.

NMR Assignments: ^{1}H NMR (300 MHz) δ 6.08 (dd, *J* = 17.5, 10.7 Hz, 2 H, C2-H), 5.23 (d, *J* = 17.5 Hz, 2 H, C1-H), 5.18 (d, *J* = 10.7 Hz, 2 H, C1-H), 4.69 (br s, 1 H, C6-H), 1.65 (s, 3 H, C4-H); ^{13}C NMR (65 MHz) δ 171.0 (C5), 140.2 (C1), 131.9 (C6), 114.1 (C2), 82.6 (C3), 20.8 (C4).

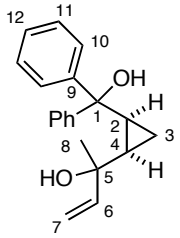


2.8

[1S-(1α,5α)]-4-Methyl-4-vinyl-3-oxabicyclo[3.1.0]hexan-2-one (2.8) (BLA-I-189). A solution of **2.9** (23 mg, 0.137 mmol) in CH_2Cl_2 (7 mL) was added to a refluxing solution of Rh_2(5*R*-MEPY)$_4$ (13 mg, 13.7 μmol) in CH_2Cl_2 (114 mL) over 17 h using a syringe pump. The resulting mixture was heated under reflux for 4 h and then allowed to cool to room temperature. The mixture was concentrated under reduced pressure and a crude ^{1}H NMR spectra indicated a mixture (1:1) of endo and exo isomers. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (1:1) to give 19 mg (99%) of **2.8** as a clear, colorless oil (combined mass of both isomers isolated). **Isomer A:** ^{1}H NMR (300 MHz) δ 5.98 (dd, *J* = 17.2, 10.7 Hz, 1 H), 5.37 (d, *J* = 17.2 Hz, 1 H), 5.18 (d, *J* = 10.7 Hz, 1 H), 2.16-2.04 (m, 2 H), 1.44 (s, 3 H), 1.17 (ddd, *J* = 8.8, 7.6, 5.0 Hz, 1 H), 1.00 (dt, *J* = 5.0, 3.2 Hz, 1 H); ^{13}C NMR (65 MHz) δ 174.3, 133.0, 119.0,

66.7, 31.6, 29.8, 28.3, 21.5; IR ($CHCl_3$) 2987, 1769, 1453, 1413, 1313, 1248, 1196, 1044, 959, 838 cm^{-1} mass spectrum (CI) *m/z* 139.0764 [$C_8H_{11}O_2$ (M+1) requires 139.0759] 139 (base). **Isomer B:** ^{1}H NMR (300 MHz) □ 5.85 (dd, *J* = 17.3, 10.9 Hz, 1 H), 5.27 (dd, *J* = 17.3, 1.0 Hz, 1 H), 5.15 (dd, *J* = 10.9, 1.0 Hz, 1 H), 2.21-2.04 (m, 2 H), 1.55 (s, 3 H), 1.14 (ddd, *J* = 8.8, 7.6, 4.9 Hz, 1 H), 0.88 (dt, *J* = 4.9, 3.4 Hz, 1 H).

NMR Assignments. Isomer A: ^{1}H NMR (300 MHz) □ 5.98 (dd, *J* = 17.2, 10.7 Hz, 1 H, C6-H), 5.37 (d, *J* = 17.2 Hz, 1 H, C7-H), 5.18 (d, *J* = 10.7 Hz, 1 H, C7-H), 2.16-2.04 (m, 2 H, C2-C3-H), 1.44 (s, 3 H, C8-H), 1.17 (ddd, *J* = 8.8, 7.6, 5.0 Hz, 1 H, C1-H), 1.00 (dt, *J* = 5.0, 3.2 Hz, 1 H, C1-H); ^{13}C NMR (65 MHz) □ 174.3 (C4), 133.0 (C6), 119.0 (C7), 66.7 (C5), 31.6 (C1), 29.8 (C3), 28.3 (C2), 21.5 (C8). **Isomer B:** ^{1}H NMR (300 MHz) □ 5.85 (dd, *J* = 17.3, 10.9 Hz, 1 H, C6-H), 5.27 (dd, *J* = 17.3, 1.0 Hz, 1 H, C7-H), 5.15 (dd, *J* = 10.9, 1.0 Hz, 1 H, C7-H), 2.21-2.04 (m, 2 H, C2-C3-H), 1.55 (s, 3 H, C8-H), 1.14 (ddd, *J* = 8.8, 7.6, 4.9 Hz, 1 H, C1-H), 0.88 (dt, *J* = 4.9, 3.4 Hz, 1 H, C1-H).

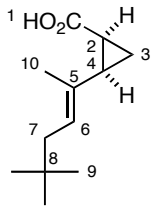


2.39

2-((1R,2S)-2-(hydroxydiphenylmethyl)cyclopropyl)but-3-en-2-ol (2.39) (BLA-VIII-152). A 1.0 M solution of PhLi in THF (0.58 mL, 0.58 mmol) was added to a stirred solution of **2.38** (20 mg, 0.14 mmol) in THF (1.5 mL) at 0 ˚C, the cooling bath was removed, and the mixture was stirred for 1.5 h. It was then cooled to 0 ˚C, and saturated aqueous $NaHCO_3$ (2 mL) was added. The layers were separated, and the

aqueous phase was extracted with Et_2O (3 x 2 mL). The organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give 38 mg (92%) of **2.39** as a mixture (1:1) of diastereomers as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.69-7.66 (comp, 2 H), 7.42-7.39 (comp, 2 H), 7.38-7.31 (comp, 2 H), 7.28-7.23 (comp, 3 H), 7.17 (app tt, *J* = 7.5, 1.5 Hz, 1 H), 6.02 (dd, *J* = 17.5, 11.0 Hz, 1 H), 5.19 (dd, *J* = 17.5, 1.0 Hz, 1 H), 5.02 (dd, *J* = 11.0, 1.0 Hz, 1 H), 1.98 (ddd, *J* = 16.5, 9.0, 7.0 Hz, 1 H), 1.23 (ddd, *J* = 12.5, 7.5, 5.0 Hz, 1 H), 1.11 (ddd, *J* = 16.5, 9.0, 7.5 Hz, 1 H), 0.95 (s, 3 H), 0.80 (ddd, *J* = 14.0, 9.0, 5.0 Hz, 1 H); ^{13}C NMR (125 MHz) δ 149.3, 149.0, 145.5, 127.8, 127.8, 126.8, 126.7, 126.6, 126.2, 111.3, 75.2, 72.0, 30.8, 28.7, 28.4, 3.11; IR (CH_2Cl_2) 3585, 3366, 3003, 1598, 1491, 1448, 1185, 1062, 924 cm^{-1}; mass spectrum (CI) *m/z* 239.1499 [$C_{20}H_{21}O_2$ (M+1) requires 239.1541] 277 (base), 259, 199, 193; HPLC (Chiracel AD column, hexanes/isopropanol = 98:2, flow = 0.5 mL/min, t_R = 60.8, 62.7, 73.1, 78.1 min).

NMR Assignments: ^{1}H NMR (500 MHz) δ 7.69-7.66 (comp, 2 H, C_{AR}-H), 7.42-7.39 (comp, 2 H, C_{AR}-H), 7.38-7.31 (comp, 2 H, C_{AR}-H), 7.28-7.23 (comp, 3 H, C_{AR}-H), 7.17 (app tt, *J* = 7.5, 1.5 Hz, 1 H, C_{AR}-H), 6.02 (dd, *J* = 17.5, 11.0 Hz, 1 H, C6-H), 5.19 (dd, *J* = 17.5, 1.0 Hz, 1 H, C7-H), 5.02 (dd, *J* = 11.0, 1.0 Hz, 1 H, C7-H), 1.98 (ddd, *J* = 16.5, 9.0, 7.0 Hz, 1 H, C2-H), 1.23 (ddd, *J* = 12.5, 7.5, 5.0 Hz, 1 H, C4-H), 1.11 (ddd, *J* = 16.5, 9.0, 7.5 Hz, 1 H, C3-H), 0.95 (s, 3 H, C8-H), 0.80 (ddd, *J* = 14.0, 9.0, 5.0 Hz, 1 H, C3-H); ^{13}C NMR (125 MHz) δ 149.3 (C9), 149.0 (C9), 145.5 (C6), 127.8, 127.8, 126.8, 126.7, 126.6, 126.2, 111.3 (C7), 75.2 (C1), 72.0 (C5), 30.8, 28.7, 28.4, 3.11 (C3).

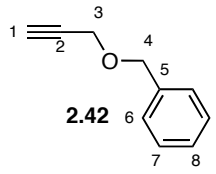


2.40

(2*S*,3*S*)-(2-(1,4,4-Trimethylpent-1-enyl)cyclopropanecarboxylic acid (2.40). (BLA-IV-49). A 1.40 M solution of *t*-BuLi in pentane (0.31 mL, 0.43 mmol) was added to a solution of CuCN (20 mg, 0.22 mmol) in degassed THF (1 mL) at –78 ˚C, and the resulting slurry was allowed to warm slowly to 0 ˚C with stirring (approx. 10 min). This yellow solution was then transferred *via* cannula to a solution of **2.8** (20 mg, 0.14 mmol) in degassed THF (0.5 mL) at 0 ˚C, the solution was allowed to warm to room temperature by removal of the cooling bath and stirred for 4 h. The mixture was then cooled to 0 ˚C and saturated aqueous NH_4Cl/NH_4OH (9:1, 2 mL) was added. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 2 mL), the combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give 22 mg (80%) of **2.40** as a mixture (2.3:1) of trans and cis isomers as a clear, colorless oil: ***trans isomer:*** ^{1}H NMR (400 MHz) □ 5.43-5.40 (m, 1 H), 2.06-1.79 (m, 4 H), 1.62 (d, *J* = 0.7 Hz, 3 H), 1.43 (app dt, *J* = 7.8, 5.2 Hz, 1 H), 1.11 (ddd, *J* = 12.4, 7.6, 4.8 Hz, 1 H), 0.86 (s, 9 H); ^{13}C NMR (100 MHz) □ 177.9, 130.1, 126.0, 41.8, 31.7, 30.7, 29.2, 19.6, 17.1, 12.0; IR ($CHCl_3$) 3689, 3022, 1602, 1226 cm^{-1}; mass spectrum (CI) *m/z* 197.1543 [$C_{12}H_{21}O_2$ (M+1) requires 197.1542] 393, 197 (base), 179, 151, 141, 125.

NMR Assignments: : ***trans isomer:*** ^{1}H NMR (400 MHz) □ 5.43-5.40 (m, 1 H, C6-H), 2.06-1.79 (m, 4 H, C2-C4-C7-H), 1.62 (d, *J* = 0.7 Hz, 3 H, C10-H), 1.43 (app dt, *J* = 7.8, 5.2 Hz, 1 H, C3-H), 1.11 (ddd, *J* = 12.4, 7.6, 4.8 Hz, 1 H, C3-H), 0.86 (s, 9 H,

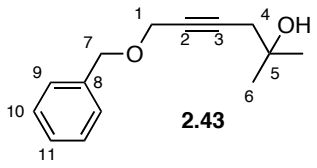
C8-H); ^{13}C NMR (100 MHz) 177.9 (C1), 130.1 (C5), 126.0 (C6), 41.8 (C7), 31.7 (C8), 30.7 (C2), 29.2 (C9), 19.6 (C4), 17.1 (C10), 12.0 (C3).



Prop-2-ynyloxymethyl-benzene (2.42) (BLA-III-170). NaH (1.094 g of a 60% mineral oil suspension, 27.3 mmol) was added to a stirred solution of propargyl alcohol **2.41** (1.534 g, 27.3 mmol) in dry DMF (50 mL) at –10 ˚C, and stirring was continued for 30 min. TBAI (505 mg, 1.37 mmol) and benzyl bromide (1.63 mL, 13.6 mmol) were added sequentially, and the reaction was allowed to warm to room temperature. The resulting dark brown solution was stirred for an additional 2 h. H_2O (20 mL) and 10 % HCl (20 mL) were then added, the layers were separated, and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic fractions were washed sequentially with saturated aqueous NaCl (100 mL) and saturated aqueous NH_4Cl (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes to give 1.934 g (97%) of **2.42** as a clear, yellow oil: ^{1}H NMR (400 MHz) 7.34-7.26 (m, 5 H), 4.58 (s, 2 H), 4.14 (d, J = 2.4 Hz, 2 H), 2.45-2.44 (m, 1 H); ^{13}C NMR (100 MHz) 137.0, 128.2, 127.8, 127.6, 79.5, 74.6, 71.4, 56.9; IR (neat) 3291, 3031, 2856, 2116, 1496, 1454, 1355, 1074 cm^{-1}; mass spectrum (CI) m/z 147.0804 [$C_{10}H_{11}O_1$ (M+1) requires 147.0810] 161, 147, 123, 107, 105, 91 (base).

NMR Assignments: ^{1}H NMR (400 MHz) δ 7.34-7.26 (m, 5 H, C6-C7-C8-H), 4.58 (s, 2 H, C4-H), 4.14 (d, J = 2.4 Hz, 2 H, C3-H), 2.45-2.44 (m, 1 H, C1-H); ^{13}C NMR (100 MHz) δ 137.0 (C4), 128.2 (C7), 127.8 (C6), 127.6 (C5), 79.5 (C8), 74.6 (C3), 71.4 (C1), 56.9 (C2).

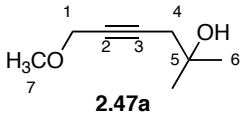
General procedure for the lithium acetylide addition to isobutylene oxide. A solution of *n*-BuLi in hexanes at the indicated molarity (2 mmol) was added to a stirred solution of protected propargyl alcohol (2 mmol) in THF (2.5 mL) at –78 ˚C, and the resulting yellow solution was stirred for 1 h. A solution of isobutylene oxide (72.1 mg, 0.089 mL, 1 mmol) in THF (2.5 mL) freshly distilled BF_3•OEt_2 (283 mg, 0.25 mL, 2 mmol) were added and the reaction was stirred for 7 h at –78 ˚C. The solution was allowed to warm to room temperature by removal of the cooling bath and stirred for an additional 40 min. Saturated aqueous $NaHCO_3$ (5 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 5 mL), and the combined organic fractions were washed with saturated aqueous NaCl (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to yield the desired homopropargylic alcohol.



2.43

6-Benzyloxy-2-methyl-4-hexyn-2-ol (2.43) (BLA-III-286). A 1.9M solution of *n*-BuLi in hexanes was used to provide alcohol **2.43** in 100% yield (4.48 mmol scale) as a clear, yellow oil: ^{1}H NMR (400 MHz) 7.34-7.25 (m, 5 H), 4.58 (s, 2 H), 4.18 (t, *J* = 2.0 Hz, 2 H), 2.42 (t, *J* = 2.0 Hz, 2 H), 2.29 (br s, 1H), 1.31 (s, 6 H); ^{13}C NMR (100 MHz) 137.2, 128.2, 127.8, 127.6, 83.5, 78.7, 71.4, 69.9, 57.5, 34.4, 28.7; IR (neat) 3416, 3031, 2973, 2930, 2858, 2282, 2220, 1496, 1454, 1359 cm^{-1}; mass spectrum (CI) *m/z* 219.1374 [$C_{14}H_{19}O_2$ (M+1) requires 219.1385] 237, 219, 183, 171 (base), 161, 143.

NMR Assignments: ^{1}H NMR (400 MHz) 7.34-7.25 (m, 5 H, C10-C11-C12-H), 4.58 (s, 2 H, C8-H), 4.18 (t, *J* = 2.0 Hz, 2 H, C7-H), 2.42 (t, *J* = 2.0 Hz, 2 H, C3-H), 2.29 (br s, 1H, O-H), 1.31 (s, 6 H, C1-C7-H); ^{13}C NMR (100 MHz) 137.2 (C9), 128.2 (C12), 127.8 (C11), 127.6 (C10), 83.5 (C6), 78.7 (C5), 71.4 (C7), 69.9 (C8), 57.5 (C2), 34.4 (C3), 28.7 (C1).

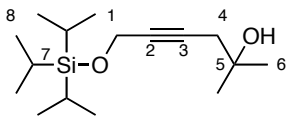


2.47a

6-Methoxy-2-methylhex-4-yn-2-ol (2.47a) (BLA-IV-106). A 2.0 M solution of *n*-BuLi in hexanes was used to provide alcohol **2.47a** in 96% yield (5.50 mmol scale) as a clear, colorless oil: ^{1}H NMR (400 MHz) 4.11 (t, *J* = 2.0 Hz, 2 H), 3.38 (s, 3 H), 2.43 (t, *J* = 2.0 Hz, 2 H), 1.32 (s, 6 H); ^{13}C NMR (100 MHz) 83.5, 78.3, 69.8, 60.0, 57.3, 34.3,

28.6; IR ($CHCl_3$) 3600, 3016, 2978, 1464, 1375, 1091 cm^{-1}; mass spectrum (CI) *m/z* 143.1071 [$C_8H_{15}O_2$ (M+1) requires 143.1072] 143, 125 (base), 95.

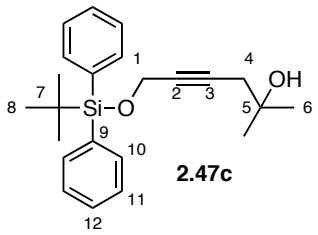
NMR Assignments: ^{1}H NMR (400 MHz) 4.11 (t, *J* = 2.0 Hz, 2 H, C1-H), 3.38 (s, 3 H, C7-H), 2.43 (t, *J* = 2.0 Hz, 2 H, C4-H), 1.32 (s, 6 H, C6-H); ^{13}C NMR (100 MHz) 83.5 (C3), 78.3 (C2), 69.8 (C5), 60.0 (C1), 57.3 (C7), 34.3 (C4), 28.6 (C6).



2.47b

6-Benzyloxy-2-methyl-4-hexyn-2-ol (2.47b) (BLA-III-286). A 1.9M solution of *n*-BuLi in hexanes was used to provide alcohol **2.47b** in 100% yield (4.48 mmol scale) as a clear, yellow oil: ^{1}H NMR (400 MHz) 7.34-7.25 (comp, 5 H), 4.58 (s, 2 H), 4.18 (t, *J* = 2.0 Hz, 2 H), 2.42 (t, *J* = 2.0 Hz, 2 H), 2.29 (br s, 1H), 1.31 (s, 6 H); ^{13}C NMR (100 MHz) 137.2, 128.2, 127.8, 127.6, 83.5, 78.7, 71.4, 57.5, 34.4, 28.7; IR (neat) 3416, 3031, 2973, 2930, 2858, 2282, 2220, 1496, 1454, 1359 cm^{-1}; mass spectrum (CI) *m/z* 219.1374 [$C_{14}H_{19}O_2$ (M+1) requires 219.1385] 237, 219, 183, 171 (base), 161, 143.

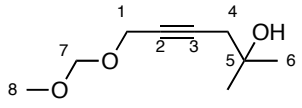
NMR Assignments: ^{1}H NMR (400 MHz) 7.34-7.25 (comp, 5 H, C9-C10-C11-H), 4.58 (s, 2 H, C7-H), 4.18 (t, *J* = 2.0 Hz, 2 H, C1-H), 2.42 (t, *J* = 2.0 Hz, 2 H, C4-H), 2.29 (br s, 1H, O-H), 1.31 (s, 6 H, C6-H); ^{13}C NMR (100 MHz) 137.2 (C8), 128.2 (C11), 127.8 (C10), 127.6 (C9), 83.5 (C1), 78.7 (C3), 71.4 (C2), 57.5 (C5), 34.4 (C4), 28.7 (C6).



2.47c

6-(*tert*-Butyldiphenylsilanyloxy)-2-methylhex-4-yn-2-ol (2.47c) (BLA-IV-169). A 2.2 M solution of *n*-BuLi in hexanes was used to provide alcohol **2.47c** in 100% yield (2.09 mmol scale) as a clear, colorless oil: ^{1}H NMR (400 MHz) 7.70 (ddd, *J* = 6.2, 1.4, 1.4 Hz, 4 H), 7.45-7.36 (comp, 6 H), 4.35 (t, *J* = 2.1 Hz, 2 H), 2.34 (t, *J* = 2.1 Hz, 2 H), 1.72 (s, 1H), 1.25 (s, 6 H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz) 135.4, 133.0, 129.6, 127.5, 81.9, 81.4, 69.8, 52.8, 34.5, 28.6, 26.7, 19.2; IR ($CHCl_3$) 3568, 3054, 2964, 2860, 1472, 1427, 1374, 1264, 1214, 1112, 1073 cm^{-1}; mass spectrum (CI) *m/z* 365.1934 [$C_{23}H_{29}O_2Si$ (M+1) requires 365.1936] 365, 349 (base), 309, 289.

NMR Assignments: ^{1}H NMR (400 MHz) 7.70 (ddd, *J* = 6.2, 1.4, 1.4 Hz, 4 H, C10-H), 7.45-7.36 (comp, 6 H, C11-C12-H), 4.35 (t, *J* = 2.1 Hz, 2 H, C1-H), 2.34 (t, *J* = 2.1 Hz, 2 H, C4-H), 1.72 (s, 1H, O-H), 1.25 (s, 6 H, C6-H), 1.05 (s, 9 H, C8-H); ^{13}C NMR (100 MHz) 135.4 (C10), 133.0 (C9), 129.6 (C12), 127.5 (C11), 81.9 (C3), 81.4 (C2), 69.8 (C5), 52.8 (C1), 34.5 (C4), 28.6 (C6), 26.7 (C8), 19.2 (C7).

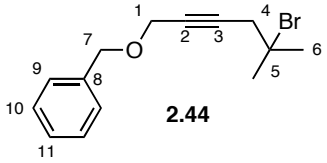


2.47d

6-Methoxymethoxy-2-methylhex-4-yn-2-ol (2.47d) (BLA-IV-91). A 2.16 M solution of *n*-BuLi in hexanes was used to provide alcohol **2.47d** in 97% yield (2.77

mmol scale) as a clear, colorless oil: ^{1}H NMR (400 MHz) δ 4.72 (s, 2 H), 4.24 (t, *J* = 2.0 Hz, 2 H), 3.39 (s, 3 H), 2.42 (t, *J* = 2.0 Hz, 2 H), 1.31 (s, 6 H); ^{13}C NMR (100 MHz) δ 94.4, 83.3, 78.0, 69.8, 55.4, 54.6, 34.3, 28.6; IR ($CHCl_3$) 3583, 2977, 1464, 1375, 1149, 1045 cm^{-1}; mass spectrum (CI) *m/z* 173.1176 [$C_9H_{17}O_3$ (M+1) requires 173.1178] 173, 141, 125 (base).

NMR Assignments: ^{1}H NMR (400 MHz) δ 4.72 (s, 2 H, C7-H), 4.24 (t, *J* = 2.0 Hz, 2 H, C1-H), 3.39 (s, 3 H, C8-H), 2.42 (t, *J* = 2.0 Hz, 2 H, C4-H), 1.31 (s, 6 H, C6-H); ^{13}C NMR (100 MHz) δ 94.4 (C7), 83.3 (C3), 78.0 (C2), 69.8 (C5), 55.4 (C1), 54.6 (C8), 34.3 (C4), 28.6 (C6).



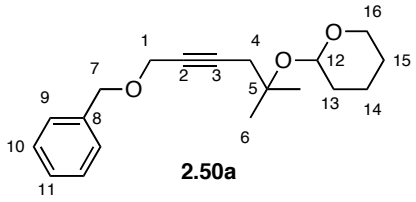
2.44

6-Benzyloxy-2-bromo-2-methyl-4-hexyne (2.44) (BLA-III-291). Trimethylsilyl bromide (0.12 mL, 0.916 mmol) was added to a solution of **2.43** (50 mg, 0.229 mmol) in CH_2Cl_2 (3 mL) at room temperature, and the reaction was stirred for 4 h. The mixture was warmed to 50 ˚C (bath temperature), stirred for an additional 2 h and allowed to cool to room temperature by removal of the cooling bath. The reaction was diluted with saturated aqueous $NaHCO_3$ (3 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 12 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (20:1) to give 15 mg (23%) of **2.44** as a clear, colorless oil: ^{1}H NMR (400 MHz) δ 7.38-7.26 (m, 5 H), 4.61 (s, 2 H), 4.19 (t, *J* =

2.0 Hz, 2 H), 2.86 (t, *J* = 2.0 Hz, 2 H), 1.85 (s, 6 H); ^{13}C NMR (100 MHz) 137.2, 128.3, 128.0, 127.7, 83.1, 78.9, 71.3, 62.4, 57.4, 38.3, 33.6; IR ($CDCl_3$) 2969, 2926, 2859, 2259, 1721, 1453, 1371, 1264, 1107, 1070, 707 cm^{-1}; mass spectrum (CI) *m/z* 279.0378 [$C_{14}H_{16}O_1Br$ (M-1) requires 279.0384] 281, 279, 265, 263, 201, 183, 171 (base).

NMR Assignments: ^{1}H NMR (400 MHz) 7.38-7.26 (m, 5 H, C10-C11-C12-H), 4.61 (s, 2 H, C7-H), 4.19 (t, *J* = 2.0 Hz, 2 H, C1-H), 2.86 (t, *J* = 2.0 Hz, 2 H, C4-H), 1.85 (s, 6 H, C1-C6-H); ^{13}C NMR (100 MHz) 137.3 (C8), 128.3 (C11), 128.0 (C10), 127.7 (C9), 83.1 (C3), 78.9 (C2), 71.3 (C7), 62.4 (C5), 57.4 (C1), 38.4 (C4), 33.6 (C6).

General procedure for the protection of tertiary alcohols as their tetrahydropyranyl ethers. Pyridinum *p*-toluenesulfonate (25 mg, 0.1 mmol) was added to a solution of dihydropyran (168 mg, 0.18 mL, 2 mmol) and homopropargylic alcohol (1 mmol) in CH_2Cl_2 (10 mL) at room temperature, and the resulting solution was stirred for 8 h. Et_2O (10 mL) was added, and the solution was washed with saturated aqueous NaCl (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (5:1) to yield the desired tetrahydropyranyl ether.

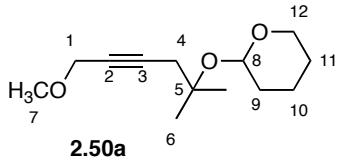


2.50a

2-(5-Benzyloxy-1,1-dimethylpent-3-ynyloxy)tetrahydropyran (2.50a) (BLA-IV-177). Ether **2.50a** was obtained in 99% yield (0.46 mmol scale) as a clear, colorless

oil: ^{1}H NMR (400 MHz) δ 7.37-7.28 (comp, 5 H), 4.82 (dd, *J* = 5.6, 3.2 Hz, 1 H), 4.60 (s, 2 H), 4.18 (t, *J* = 2.4 Hz, 2 H), 3.97 (ddd, *J* = 11.2, 4.8, 2.8 Hz, 1 H), 3.45 (app dt, *J* = 11.2, 4.8 Hz, 1 H), 2.54 (dt, *J* = 16.8, 2.4 Hz, 1 H), 2.47 (dt, *J* = 16.8, 2.4 Hz, 1 H), 1.84-1.47 (comp, 6 H), 1.36 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR (100 MHz) δ 137.5, 128.3, 128.0, 127.7, 94.5, 84.3, 75.6, 71.2, 63.1, 62.8, 57.6, 32.4, 30.6, 26.2, 26.0, 25.3, 19.6; IR ($CDCl_3$) 2946, 2854, 2247, 1722, 1454, 1385, 1354, 1129, 1073, 1030 cm^{-1}; mass spectrum (CI) *m/z* 303.1946 [$C_{19}H_{27}O_3$ (M+1) requires 303.1960] 303 (base).

NMR Assignments: ^{1}H NMR (400 MHz) δ 7.37-7.28 (comp, 5 H, C9-C10-C11-H), 4.82 (dd, *J* = 5.6, 3.2 Hz, 1 H, C12-H), 4.60 (s, 2 H, C7-H), 4.18 (t, *J* = 2.4 Hz, 2 H, C2-H), 3.97 (ddd, *J* = 11.2, 4.8, 2.8 Hz, 1 H, C13-H), 3.45 (app dt, *J* = 11.2, 4.8 Hz, 1 H, C13-H), 2.54 (dt, *J* = 16.8, 2.4 Hz, 1 H, C4-H), 2.47 (dt, *J* = 16.8, 2.4 Hz, 1 H, C4-H), 1.84-1.47 (comp, 6 H, C14-C15-C16-H), 1.36 (s, 3 H, C6-H), 1.34 (s, 3 H, C6-H); ^{13}C NMR (100 MHz) δ 137.5 (C8), 128.3, 128.0, 127.7, 94.5 (C12), 84.3 (C3), 75.6 (C2), 71.2 (C7), 63.1 (C13), 62.8 (C5), 57.6 (C1), 32.4 (C16), 30.6 (C4), 26.2 (C6), 26.0 (C6), 25.3 (C14), 19.6 (C15).

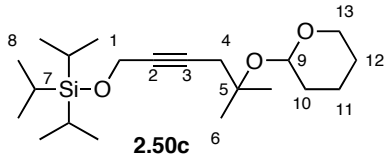


2.50a

2-(5-Methoxy-1,1-dimethylpent-3-ynyloxy)tetrahydropyran (2.50a) (BLA-IV-114). Ether **2.50a** was obtained in 76% yield (0.70 mmol scale) as a clear, colorless oil: ^{1}H NMR (400 MHz) δ 4.80 (dd, *J* = 5.2, 2.8 Hz, 1 H), 4.09 (t, *J* = 2.4 Hz, 2 H), 3.96 (ddd, *J* = 11.6, 5.1, 3.4 Hz, 1 H), 3.45 (app dt, *J* = 11.6, 5.5 Hz, 1 H), 3.37 (s, 3 H), 2.52 (app

dt, *J* = 16.4, 2.0 Hz, 1 H), 2.44 (app dt, *J* = 16.4, 2.0 Hz, 1 H), 1.89-1.79 (m, 1 H), 1.70-1.62 (m, 1 H), 1.57-1.46 (m, 4 H), 1.34 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (100 MHz) 93.9, 84.1, 77.4, 75.6, 63.1, 60.1, 57.3, 32.4, 32.2, 26.3, 26.1, 25.4, 20.6; IR ($CDCl_3$) 3690, 3607, 2939, 2247, 1717, 1601, 1441, 1375, 1276, 1129, 1075, 1031 cm^{-1}; mass spectrum (CI) *m/z* 227.1651 [$C_{13}H_{23}O_3$ (M+1) requires 227.1647] 242, 227 (base), 211, 167.

NMR Assignments: ^{1}H NMR (400 MHz) 4.80 (dd, *J* = 5.2, 2.8 Hz, 1 H, C8-H), 4.09 (t, *J* = 2.4 Hz, 2 H, C1-H), 3.96 (ddd, *J* = 11.6, 5.1, 3.4 Hz, 1 H, C12-H), 3.45 (app dt, *J* = 11.6, 5.5 Hz, 1 H, C12-H), 3.37 (s, 3 H, C7-H), 2.52 (app dt, *J* = 16.4, 2.0 Hz, C4-H), 2.44 (app dt, *J* = 16.4, 2.0 Hz, 1 H, C4-H), 1.89-1.79 (m, 1 H, C9-H), 1.70-1.62 (m, 1 H, C9-H), 1.57-1.46 (m, 4 H, C10-C11-H), 1.34 (s, 3 H, C6-H), 1.33 (s, 3 H, C6-H); ^{13}C NMR (100 MHz) 93.9 (C8), 84.1 (C3), 77.4 (C2), 75.6 (C12), 63.1 (C5), 60.1 (C1), 57.3 (C7), 32.4 (C9), 32.2 (C4), 26.3 (C6), 26.1 (C6), 25.4 (C11), 20.6 (C10).



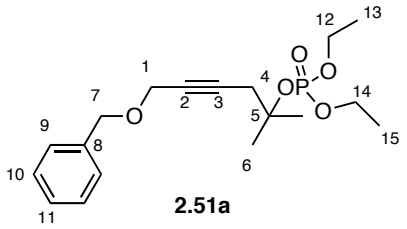
2.50c

Triisopropyl[5-methyl-5-(tetrahydropyran-2-yloxy)hex-2-ynyloxy]silane (2.50c) (BLA-IV-95). Ether **2.50c** was obtained in 96% yield (0.18 mmol scale) as a clear, colorless oil: ^{1}H NMR (400 MHz) 4.79 (ddd, *J* = 5.5, 3.1, 3.1 Hz, 1 H), 4.37 (t, *J* = 2.4 Hz, 2 H), 3.95 (ddd, *J* = 11.3, 5.1, 3.1 Hz, 1 H), 3.44 (app dt, *J* = 11.2, 5.5 Hz, 1 H), 2.50 (app dt, *J* = 16.4, 2.0 Hz, 1 H), 2.42 (app dt, *J* = 16.4, 2.0 Hz, 1 H), 1.84 (app ddt, *J* = 11.6, 9.6, 2.0 Hz, 1 H), 1.66 (app ddt, *J* = 11.6, 9.6, 2.0 Hz, 1 H), 1.55-1.46 (m, 4 H),

1.33 (s, 1 H), 1.31 (s, 1 H), 1.15-1.06 (comp, 21 H); ^{13}C NMR (100 MHz) δ 94.1, 82.1, 80.4, 75.8, 63.2, 52.1, 32.5, 32.3, 26.3, 26.1, 25.5, 20.7, 18.0, 12.1; IR ($CHCl_3$) 2945, 2866, 1464, 1370, 1260, 1224, 1141, 1074, 1030 cm^{-1}; mass spectrum (CI) *m/z* 369.2811 [$C_{21}H_{41}O_3Si$ (M+1) requires 369.2824] 369 (base), 325.

NMR Assignments: ^{1}H NMR (400 MHz) δ 4.79 (ddd, *J* = 5.5, 3.1, 3.1 Hz, 1 H, C9-H), 4.37 (t, *J* = 2.4 Hz, 2 H, C1-H), 3.95 (ddd, *J* = 11.3, 5.1, 3.1 Hz, 1 H, C13-H), 3.44 (app dt, *J* = 11.2, 5.5 Hz, 1 H, C13-H), 2.50 (app dt, *J* = 16.4, 2.0 Hz, 1 H, C4-H), 2.42 (app dt, *J* = 16.4, 2.0 Hz, 1 H, C4-H), 1.84 (app ddt, *J* = 11.6, 9.6, 2.0 Hz, 1 H, C10-H), 1.66 (app ddt, *J* = 11.6, 9.6, 2.0 Hz, 1 H, C10-H), 1.55-1.46 (m, 4 H, C11-C12-H), 1.33 (s, 1 H, C6-H), 1.31 (s, 1 H, C6-H), 1.15-1.06 (comp, 21 H, C7-C8-H); ^{13}C NMR (100 MHz) δ 94.1 (C9), 82.1 (C3), 80.4 (C2), 75.8 (C13), 63.2 (C5), 52.1 (C1), 32.5 (C10), 32.3 (C4), 26.3 (C6), 26.1 (C6), 25.5 (C12), 20.7 (C11), 18.0 (C8), 12.1 (C7).

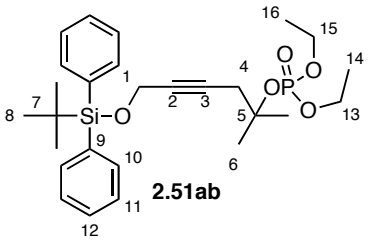
General procedure for the synthesis of homopropargylic diethyl phosphates from tertiary alcohols. A solution of *n*-BuLi in hexanes at the indicated molarity (0.92 mmol) was added to a solution of homopropargylic alcohol (0.92 mmol) in THF (9 mL) at –78 ˚C, and the resulting yellow solution was stirred for 1 h. Diethyl chlorophosphate (0.20 mL, 1.37 mmol) was added *via* syringe and the reaction was allowed to warm slowly to room temperature by removal of the cooling bath and stirred for the indicated time. Saturated aqueous $NaHCO_3$ (9 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL), and the combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to yield the desired phosphate.



2.51a

Phosphoric acid 5-benzyloxy-1,1-dimethylpent-3-ynyl ester diethyl ester (2.51a) (BLA-IV-206). A 2.23 M solution of *n*-BuLi in hexanes was used to provide **2.51a** in 68% yield (0.92 mmol scale) after 24 h as a clear, colorless oil: ^{1}H NMR (400 MHz) 7.36-7.30 (comp, 5 H), 4.59 (s, 2 H), 4.17 (t, *J* = 2.0 Hz, 2 H), 4.09 (app ddt, *J* = 14.8, 14.4, 7.2 Hz, 2 H), 2.72 (t, *J* = 2.0 Hz, 2 H), 1.60 (s, 6 H), 1.31 (ddd, *J* = 8.0, 6.8, 0.8 Hz, 3 H); ^{13}C NMR (100 MHz) 137.4, 128.4, 127.9, 127.8, 82.7, 82.5, 78.3, 71.3, 63.5, 63.4, 57.5, 33.3, 27.1, 16.1, 16.0; IR ($CDCl_3$) 2984, 2937, 2360, 2243, 1633, 1398, 1259, 1028 cm^{-1}; mass spectrum (CI) *m/z* 355.1664 [$C_{18}H_{28}O_5P$ (M+1) requires 355.1674] 355 (base).

NMR Assignments: ^{1}H NMR (400 MHz) 7.36-7.30 (comp, 5 H, C9-C10-C11-H), 4.59 (s, 2 H, C7-H), 4.17 (t, *J* = 2.0 Hz, 2 H, C1-H), 4.09 (app ddt, *J* = 14.8, 14.4, 7.2 Hz, 2 H, C12-H), 2.72 (t, *J* = 2.0 Hz, 2 H, C4-H), 1.60 (s, 6 H, C6-H), 1.31 (ddd, *J* = 8.0, 6.8, 0.8 Hz, 3 H, C13-H); ^{13}C NMR (100 MHz) 137.4 (C8), 128.4, 127.9, 127.8, 82.7 (C3), 82.5 (C2), 78.3 (C7), 71.3 (C5), 63.5 (C12), 63.4 (C14), 57.5 (C1), 33.3 (C4), 27.1 (C6), 16.1 (C13), 16.0 (C15).



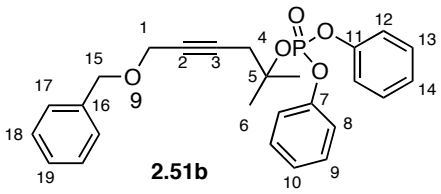
2.51ab

Phosphoric acid 5-(*tert*-butyl-diphenyl-silanyloxy)-1,1-dimethyl-pent-3-ynyl ester diethyl ester (2.51ab) (BLA-IV-202). A 2.29 M solution of *n*-BuLi in hexanes was used to provide **2.51ab** in 69% yield (0.18 mmol scale) after 8 h as a clear, colorless oil: ^{1}H NMR (400 MHz) δ 7.72 (dd, *J* = 14.4, 6.8 Hz, 4 H), 7.39 (app dt, *J* = 14.4, 6.8 Hz, 6 H), 4.32 (t, *J* = 2.0 Hz, 2 H), 4.10-4.03 (m, 2 H), 2.64 (t, *J* = 2.0 Hz, 2 H), 1.54 (s, 6 H), 1.33-1.27 (m, 6 H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz) δ 135.5, 133.1, 129.7, 127.6, 82.0, 80.8, 63.4, 63.4, 52.8, 33.2, 26.9, 26.9, 19.1, 16.0; IR ($CDCl_3$) 2984, 2932, 2860, 2245, 1728, 1472, 1428, 1391, 1257, 1147, 1112, 1029, 1006 cm^{-1}; mass spectrum (CI) *m/z* 503.2373 [$C_{27}H_{40}O_5SiP$ (M+1) requires 503.2383] 503 (base), 280, 263, 255, 239.

NMR Assignments: ^{1}H NMR (400 MHz) δ 7.72 (dd, *J* = 14.4, 6.8 Hz, 4 H, C10-H), 7.39 (app dt, *J* = 14.4, 6.8 Hz, 6 H, C11-C12-H), 4.32 (t, *J* = 2.0 Hz, 2 H, C1-H), 4.10-4.03 (m, 2 H, C13-H), 2.64 (t, *J* = 2.0 Hz, 2 H, C4-H), 1.54 (s, 6 H, C6-H), 1.33-1.27 (m, 6 H, C14-C16-H), 1.05 (s, 9 H, C8-H); ^{13}C NMR (100 MHz) δ 135.5, 133.1, 129.7, 127.6, 82.0 (C3), 80.8 (C2), 63.4 (C5), 63.4 (C13), 52.8 (C1), 33.2 (C4), 26.9 (C6), 26.9 (C6), 26.6 (C8), 19.1 (C14), 16.0 (C7).

General procedure for the synthesis of homopropargylic diphenyl phosphates from tertiary alcohols. A solution of *n*-BuLi in hexanes at the indicated molarity (0.23 mmol) was added to a solution of homopropargylic alcohol (0.23 mmol) in THF (2.3 mL) at –78 °C, and the resulting yellow solution was stirred for 1 h. Diphenyl

chlorophosphate (0.07 mL, 0.34 mmol) was added *via* syringe, and the reaction was allowed to warm to room temperature by removal of the cooling bath and stirred for the indicated time. DMAP (5.0 mg, 0.041 mmol) was then added in one portion, and the reaction was stirred for additional 12 h. Saturated aqueous $NaHCO_3$ (3 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 4 mL), and the combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (ratios given) to yield the desired phosphate.

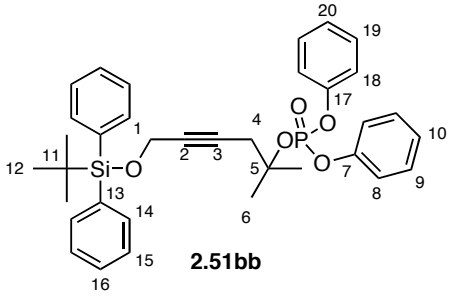


2.51b

Phosphoric acid 5-benzyloxy-1,1-dimethylpent-3-ynyl ester diphenyl ester (2.51b) (BLA-IV-213). A 2.23 M solution of *n*-BuLi in hexanes was used to provide phosphonate **2.51b** in 55% yield (0.23 mmol scale) after 12 h, followed by flash chromatography (hexanes/EtOAc = 2:1) as a clear, pale yellow oil: ^{1}H NMR (400 MHz) 7.35-7.14 (comp, 15 H), 4.56 (s, 2 H), 4.12 (t, *J* = 2.0 Hz, 2 H), 2.75 (br s, 2 H), 1.65 (s, 6 H); ^{13}C NMR (100 MHz) 150.6, 137.4, 129.6, 128.3, 128.0, 127.7, 125.0, 120.0, 85.4, 82.1, 78.8, 71.3, 57.4, 33.3, 27.1; IR ($CDCl_3$) 2985, 2248, 1594, 1490, 1284, 1192, 1025 cm^{-1}; mass spectrum (CI) *m/z* 451.1667 [$C_{26}H_{28}O_5P$ (M+1) requires 451.1674] 451 (base), 343.

NMR Assignments: ^{1}H NMR (400 MHz) 7.35-7.14 (comp, 15 H, C8-C9-C10-C12-C13-C14-C17-C18-C19-H), 4.56 (s, 2 H, C7-H), 4.12 (t, *J* = 2.0 Hz, 2 H, C1-H),

2.75 (br s, 2 H, C4-H), 1.65 (s, 6 H, C6-H); ^{13}C NMR (100 MHz) 150.6 (C12), 137.4 (C8), 129.6, 128.3, 128.0, 127.7, 125.0, 120.0, 85.4 (C3), 82.1 (C2), 78.8 (C7), 71.3 (C5), 57.4 (C1), 33.3 (C4), 27.1 (C6).

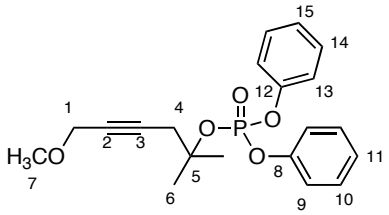


2.51bb

Phosphoric acid 5-(*tert*-butyl-diphenyl-silanyloxy)-1,1-dimethyl-pent-3-ynyl ester diphenyl ester (2.51bb) (BLA-V-63). A 2.20 M solution of *n*-BuLi in hexanes was used to provide phosphonate **2.51bb** in 66% yield (0.27 mmol scale) after 24 h, followed by flash chromatography (hexanes/EtOAc = 5:1) as a clear, pale yellow oil: ^{1}H NMR (400 MHz) 7.70 (app dt, *J* = 6.5, 1.4 Hz, 4 H), 7.38 (app dt, *J* = 13.6, 6.5, 1.4 Hz, 6 H), 7.29 (t, *J* = 8.0 Hz, 4 H), 7.21 (app dt, *J* = 7.2, 1.4 Hz, 4 H), 7.13 (ddd, *J* = 8.0, 7.2, 0.8 Hz, 2 H), 4.27 (t, *J* = 2.0 Hz, 2 H), 2.66 (t, *J* = 2.0 Hz, 2 H), 1.58 (s, 6 H), 1.04 (s, 9 H); ^{13}C NMR (100 MHz) 150.7, 150.6, 135.5, 133.1, 129.7, 129.6, 127.6, 125.0, 120.1, 120.0, 85.6, 81.2, 80.7, 52.7, 33.3, 27.0, 26.6, 19.1; IR ($CDCl_3$) 3073, 2961, 2932, 2859, 2247, 1592, 1490, 1282, 1132, 1112, 1025, 957 cm^{-1}; mass spectrum (CI) *m/z* 599.2384 [$C_{35}H_{40}O_5SiP$ (M+1) requires 599.2383] 599, 410, 349 (base), 327, 309.

NMR Assignments: ^{1}H NMR (400 MHz) 7.70 (app dt, *J* = 6.5, 1.4 Hz, 4 H, C14-H), 7.38 (app dt, *J* = 13.6, 6.5, 1.4 Hz, 6 H, C15-C16-H), 7.29 (t, *J* = 8.0 Hz, 4 H, C9-H), 7.21 (app dt, *J* = 7.2, 1.4 Hz, 4 H, C8-H), 7.13 (ddd, *J* = 8.0, 7.2, 0.8 Hz, 2 H,

C10-H), 4.27 (t, *J* = 2.0 Hz, 2 H, C1-H), 2.66 (t, *J* = 2.0 Hz, 2 H, C4-H), 1.58 (s, 6 H, C6-H), 1.04 (s, 9 H, C12-H); ^{13}C NMR (100 MHz) 150.7 (C7), 150.6 (C17), 135.5, 133.1, 129.7, 129.6, 127.6, 125.0, 120.1, 120.0, 85.6 (C3), 81.2 (C2), 80.7 (C5), 52.7 (C1), 33.3 (C4), 27.0 (C6), 26.6 (C12), 19.1 (C11).

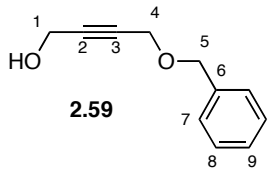


2.51bc

Phosphoric acid 5-methoxy-1,1-dimethylpent-3-ynyl ester diphenyl ester (2.51bc) (BLA-VI-41). DMAP was not used in the synthesis of this substrate. A 2.30 M solution of *n*-BuLi in hexanes was used to provide phosphonate **2.51bc** in 48% yield (1.11 mmol scale) after 24 h, followed by flash chromatography (hexanes/EtOAc = 2:1) as a clear, colorless oil: ^{1}H NMR (400 MHz) 7.33 (dd, *J* = 8.2, 8.0 Hz, 4 H), 7.24-7.22 (comp, 4 H), 7.17 (ddd, *J* = 8.2, 7.5, 1.0 Hz, 2 H), 4.04 (t, *J* = 2.0 Hz, 2 H), 3.33 (s, 3 H), 2.73 (br s, 2 H), 1.64 (s, 6 H); ^{13}C NMR (100 MHz) 150.6, 129.6, 125.0, 120.0, 85.4, 82.0, 78.6, 59.9, 57.3, 33.2, 27.0; IR ($CHCl_3$) 3016, 2361, 1592, 1490, 1284, 1192, 1162, 1093, 1025, 957, 908 cm^{-1}; mass spectrum (CI) *m/z* 375.1360 [$C_{20}H_{24}O_5P$ (M+1) requires 375.1361] 375 (base), 343.

NMR Assignments: ^{1}H NMR (400 MHz) 7.33 (dd, *J* = 8.2, 8.0 Hz, 4 H, C_{AR}-H), 7.24-7.22 (comp, 4 H, C_{AR}-H), 7.17 (ddd, *J* = 8.2, 7.5, 1.0 Hz, 2 H, C11-C15-H), 4.04 (t, *J* = 2.0 Hz, 2 H, C1-H), 3.33 (s, 3 H, C7-H), 2.73 (br s, 2 H, C4-H), 1.64 (s, 6 H, C6-

H); ^{13}C NMR (100 MHz) δ 150.6 (C8), 129.6, 125.0, 120.0, 85.4 (C3), 82.0 (C2), 78.6 (C5), 59.9 (C1), 57.3 (C7), 33.2 (C4), 27.0 (C6).

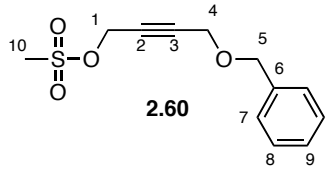


2.59

4-Benzyloxy-2-butyn-1-ol (2.59) (BLA-III-142). NaH (2.326 g of a 60% mineral oil suspension, 58.0 mmol) was added portionwise to a solution of 2-butyn-1,4-diol **2.58** (10.0 g, 116.3 mmol) in DMF (250 mL) at 0 ˚C. The resulting mixture was stirred for 30 min, whereupon TBAI (2.148 g, 5.8 mmol) and benzyl bromide (6.9 mL, 58.0 mmol) were added and the reaction allowed to warm to room temperature by removal of the cooling bath and stirred for an additional 2 h. H_2O (200 mL) and 10% HCl (200 mL) were added, and the layers separated. The aqueous phase was extracted with Et_2O (3 x 200 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 5.460 g (53%) of **2.59** as a clear, yellow oil whose spectral data was consistent with that reported in the literature:[383] ^{1}H NMR (500 MHz) δ 7.35-7.27 (comp, 5 H), 4.57 (s, 2 H), 4.30 (t, *J* = 1.8 Hz, 2 H), 4.19 (t, *J* = 1.8 Hz, 2 H), 1.82 (br s, 1 H); ^{13}C NMR (65 MHz) δ 137.1, 128.4, 128.0, 127.8, 84.7, 81.6, 71.7, 57.3, 51.0; mass spectrum (CI) *m/z* 176 (base), 154, 146.

NMR Assignments: ^{1}H NMR (500 MHz) δ 7.35-7.27 (m, 5 H, C7-C8-C9-H), 4.57 (s, 2 H, C5-H), 4.30 (t, *J* = 1.8 Hz, 2 H, C1-H), 4.19 (t, *J* = 1.8 Hz, 2 H, C4-H), 1.82

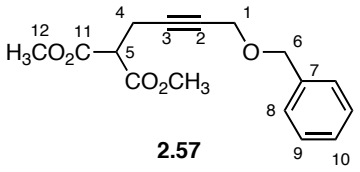
(bs, 1 H, O-H); ^{13}C NMR (65 MHz) δ 137.1 (C6) 128.4 (C9), 128.0 (C8), 127.8 (C7), 84.7 (C2), 81.6 (C3), 71.7 (C5), 57.3 (C4), 51.0 (C1).



Methylsulfonic acid 4-benzyloxy-2-butynyl ester (2.60) (BLA-III-144). Methanesulfonyl chloride (2.13 mL, 27.6 mmol) was added to a solution of **2.59** (4.410 g, 25.0 mmol) and Et_3N (5.24 mL, 37.6 mmol) in CH_2Cl_2 (100 mL) at 0 ˚C, and the solution was stirred for 20 min. The reaction was allowed to warm to room temperature by removal of the cooling bath and stirred for an additional 5 min. H_2O (100 mL) was added and the layers were separated. The aqueous phase extracted with Et_2O (3 x 100 mL). The combined organic fractions were washed with saturated aqueous NaCl (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to give 5.834 g (92%) of **2.60** as a clear, red oil: ^{1}H NMR (300 MHz) δ 7.34 (comp, 5 H), 4.92 (t, *J* = 1.5 Hz, 2 H), 4.59 (s, 2 H), 4.24 (t, *J* = 1.5 Hz, 2 H), 3.12 (s, 3 H). ^{13}C NMR (65 MHz) δ 136.8, 128.2, 127.7, 127.6, 85.6, 78.4, 71.6, 57.4, 56.8, 38.5; IR (neat) 3030, 2938, 2860, 1723, 1700, 1454, 1360 cm^{-1}; mass spectrum (CI) *m/z* 255.0686 [$C_{12}H_{15}O_4S_1$ (M+1) requires 255.0691] 255, 181, 159, 131, 129 (base).

NMR Assignments: ^{1}H NMR (500 MHz) δ 7.34 (comp, 5 H, C7-C8-C9-H), 4.92 (t, *J* = 1.5 Hz, 2 H, C1-H), 4.59 (s, 2 H, C5-H), 4.24 (t, *J* = 1.5 Hz, 2 H, C4-H), 3.12 (s, 3

H, C10-H). ^{13}C NMR (65 MHz) 136.8 (C6), 128.2 (C9), 127.7 (C8), 127.6 (C7), 85.6 (C2), 78.4 (C3), 71.6 (C5), 57.4 (C4), 56.8 (C1), 38.5 (C10).

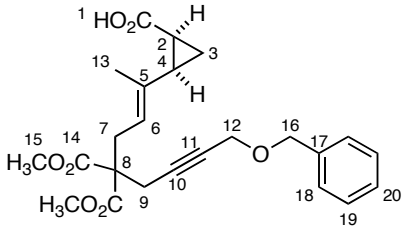


2.57

2-(4-Benzyloxy-2-butynyl)-malonic acid dimethyl ester (2.57) (BLA-II-226). Dimethyl malonate (2.58 mL, 22.6 mmol) was added to a suspension of NaH (542 mg of a 60% mineral oil suspension, 13.5 mmol) in THF (15 mL) at 0 °C, and the mixture was stirred for 25 min. A solution of **2.60** (1.147 g, 4.51 mmol) in THF (5 mL) was then added *via* syringe, and the reaction was allowed to warm to room temperature and stirred for an additional 2.5 h. The mixture was cooled to 0 ˚C, H_2O (20 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 20 mL), and the combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give 1.269 g (97%) of **3.50** as a clear, colorless oil: ^{1}H NMR (500 MHz) 7.33-7.25 (comp, 5 H), 4.53 (s, 2 H), 4.10 (t, J = 2.1 Hz, 2 H), 3.74 (s, 6 H), 3.60 (t, J = 7.6 Hz, 1 H), 2.84 (dt, J = 7.5, 2.1 Hz, 2 H); ^{13}C NMR (65 MHz) 168.3, 137.3, 128.3, 128.0, 127.7, 82.4, 79.4, 71.1, 57.2, 52.7, 23.9; IR (neat) 3031, 2954, 2853, 1738, 1454, 1345, 1071 cm^{-1}; mass spectrum (CI) m/z 291.1232 [$C_{16}H_{19}O_5$ (M+1) requires 291.1230] 261, 183.

NMR Assignments: ^{1}H NMR (500 MHz) 7.33-7.25 (comp, 5 H, C8-C9-C10-H), 4.53 (s, 2 H, C6-H), 4.10 (t, J = 2.1 Hz, 2 H, C1-H), 3.74 (s, 6 H, C12-H), 3.60 (t, J =

7.6 Hz, 1 H, C5-H), 2.84 (dt, *J* = 7.5, 2.1 Hz, 2 H, C4-H); ^{13}C NMR (65 MHz) δ 168.3 (C11), 137.3 (C8), 128.3 (C9), 128.0 (C10), 127.7 (C7), 82.4 (C3), 79.4 (C2), 71.1 (C5), 57.2 (C4), 52.7 (C6), 50.9 (C1).

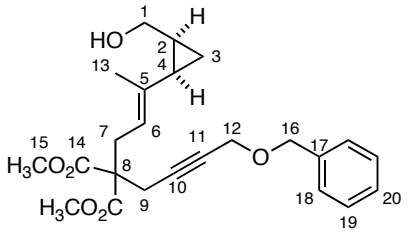


2.56

2-(4-Benzyloxy-but-2-ynyl)-2-[3-(2*S*,3*S*)-(2-carboxycyclopropyl)-but-2-enyl]-malonic acid dimethyl ester (2.56) (BLA-III-29). $Pd(PPh_3)_4$ (81 mg, 73 μmol) and PPh_3 (190 mg, 0.725 mmol) were added sequentially to a solution of **2.8** (100 mg, 0.725 mmol) in degassed THF (4 mL) at room temperature, and the resulting solution was stirred for 20 min. In a separate flask, **2.57** (462 mg, 1.59 mmol) was added to a slurry of NaH (58 mg of a 60% mineral oil suspension, 1.45 mmol) in degassed THF (4 mL) at room temperature. After stirring for 20 min at room temperature, the resulting homogeneous solution was transferred *via* cannula to the flask containing the catalyst and substrate. The mixture was heated under reflux for 4 h. The resulting dark brown solution was allowed to cool to room temperature by removal of the oil bath and then cooled to 0 ˚C. Aqueous 1M $NaHSO_4$ (8 mL) was added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1 to 1:1) to give 220 mg (71%) of **2.56**

as a clear, yellow oil: ^{1}H NMR (500 MHz) 7.35-7.27 (comp, 5 H), 5.13 (t, *J* = 7.4, 1.5 Hz, 1 H), 4.57 (s 2 H), 4.07 (t, *J* = 1.0 Hz, 6 H), 3.68 (s, 3 H), 3.66 (s, 3 H), 2.83 (br s, 2 H, C9-H), 2.81 (br s, 2 H, C7-H), 1.95 (br q, *J* = 16.2, 8.1 Hz, 1 H), 1.81 (m, 1 H), 1.70 (s, 3H), 1.36 (m, 1 H), 1.10 (m, 1 H); ^{13}C NMR (125 MHz) 175.9, 170.5, 137.5, 128.4, 128.2, 127.8, 127.8, 121.1, 82.0, 78.8, 71.2, 57.1, 52.7, 30.7, 29.7, 22.8, 19.6, 17.3, 17.3; IR ($CDCl_3$) 2952, 2259, 1735, 1698, 1436, 1291, 1211, 1070 cm^{-1}; mass spectrum (CI) *m/z* 429.1907 [$C_{16}H_{19}O_5$ (M+1) requires 429.1913] 399, 321, 279.

NMR Assignments: ^{1}H NMR (500 MHz) 7.35-7.27 (comp, 5 H, C18-C19-C20-H), 5.13 (t, *J* = 7.4, 1.5 Hz, 1 H, C6-H), 4.57 (s 2 H, C16-H), 4.07 (t, *J* = 1.0 Hz, 6 H, C12-H), 3.68 (s, 3 H, C15-H), 3.66 (s, 3 H, C15-H), 2.83 (br s, 2 H, C9-H), 2.81 (br s, 2 H, C7-H), 1.95 (br q, *J* = 16.2, 8.1 Hz, 1 H, C2-H), 1.81 (m, 1 H, C4-H), 1.70 (s, 3H, C13-H), 1.36 (m, 1 H, C3-H), 1.10 (m, 1 H, C3-H); ^{13}C NMR (65 MHz) 175.9 (C1), 170.5 (C14), 137.5 (C17), 128.4 (C_{AR}), 128.2 (C_{AR}), 127.8 (C5,C_{AR}), 121.1 (C6), 82.0 (C11), 78.8 (C10), 71.2 (C16), 57.1 (C12), 52.7 (C15), 30.7 (C7), 29.7 (C4), 22.8 (C9), 19.6 (C2), 17.3 (C3,13).



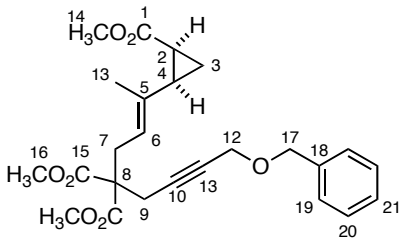
2.62

2-(4-Benzyloxybut-2-ynyl)-2-[3-(2*S*,3*S*)-2-hydroxymethylcyclopropyl)but-2-enyl]-malonic acid dimethyl ester (2.62) (BLA-III-179). Oxalyl chloride (15 L, 0.128

mmol) was added dropwise to a solution of **2.56** (25 mg, 0.058 mmol) in dry benzene (0.5 mL) at 0 ˚C. The reaction was allowed to warm to room temperature by removal of the cooling bath and stirred for 1 h. The solution was concentrated under reduced pressure, and the crude acid chloride was dissolved in dry THF (1 mL). $NaBH_4$ (5 mg, 0.12 mmol) was added in one portion with stirring at room temperature. The reaction was cooled to 0 ˚C, H_2O (0.5 mL) was added dropwise, and stirring continued for 3 h. The reaction was quenched with 1 M HCl (1 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (3 x 1 mL), and the combined organic fractions were washed with saturated aqueous NaCl (2 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give 17 mg (71%) of **2.62** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.35-7.27 (comp, 5 H), 4.99 (app ddt, *J* = 7.2, 7.0, 1.4 Hz, 1 H), 4.55 (s, 2 H), 4.13 (t, *J* = 2.2 Hz, 2 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.50 (dd, *J* = 11.2, 6.2 Hz, 1 H), 3.35 (dd, *J* = 11.2, 8.4 Hz, 1 H), 2.89 (dd, *J* = 14.7, 8.4 Hz, 1 H), 2.84 (t, *J* = 2.0 Hz, 2H), 2.81 (dd, *J* = 14.8, 7.0 Hz, 1H), 1.78 (d, *J* = 0.6 Hz, 3 H), 1.28 (app ddt, *J* = 11.0, 6.0, 2.2 Hz, 2 H), 0.72 (ddd, *J* = 13.2, 8.2, 5.2 Hz, 1 H), 0.47 (app dt, *J* = 11.4, 5.4 Hz, 1 H); ^{13}C NMR (125 MHz) δ 170.6, 170.6, 137.5, 137.2, 128.4, 128.1, 127.9, 81.6, 79.2, 71.3, 62.3, 57.4, 52.8, 30.9, 24.5, 23.2, 19.7, 18.4, 6.8; IR ($CDCl_3$) 2954, 2260, 1733, 1436, 1264, 1208, 1070 cm^{-1}; mass spectrum (CI) *m/z* 415.2115 [$C_{24}H_{31}O_6$ (M+1) requires 413.2121] 415 (base), 307, 229.

NMR Assignments: ^{1}H NMR (500 MHz) δ 7.35-7.27 (comp, 5 H, C18-C19-C20-H), 4.99 (app ddt, *J* = 7.2, 7.0, 1.4 Hz, 1 H, C6-H), 4.55 (s, 2 H, C16-H), 4.13 (t, *J* = 2.2 Hz, 2 H, C12-H), 3.74 (s, 3 H, C15-H), 3.73 (s, 3 H, C15-H), 3.50 (dd, *J* = 11.2, 6.2 Hz, 1 H, C1-H), 3.35 (dd, *J* = 11.2, 8.4 Hz, 1 H, C1-H), 2.89 (dd, *J* = 14.7, 8.4 Hz, 1 H, C7-H), 2.84 (t, *J* = 2.0 Hz, 2H, C9-H), 2.81 (dd, *J* = 14.8, 7.0 Hz, 1H, C7-H), 1.78 (d, *J* =

0.6 Hz, 3 H, C13-H), 1.28 (app ddt, J = 11.0, 6.0, 2.2 Hz, 2 H, C2-C4-H), 0.72 (ddd, J = 13.2, 8.2, 5.2 Hz, 1 H, C3-H), 0.47 (app dt, J = 11.4, 5.4 Hz, 1 H, C3-H); ^{13}C NMR (125 MHz) □ 170.6 (C14), 170.6 (C14), 137.5 (C17), 137.2 (C5), 128.4 (C20), 128.1 (C19), 127.9 (C18), 118.4 (C6), 81.6 (C11), 79.2 (C10), 71.3 (C16), 62.3 (C1), 57.4 (C12), 52.8 (C15), 30.9 (C7), 24.5 (C2), 23.2 (C9), 19.7 (C4), 18.4 (C13), 6.8 (C3).

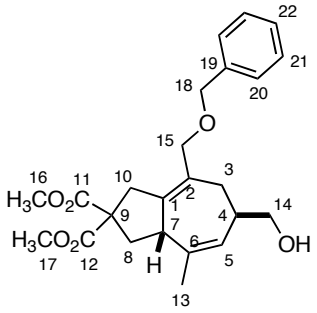


2.63

(1*S*,2*R*,*E*)-methyl 2-(9-(benzyloxy)-5,5-bis(methoxycarbonyl)non-2-en-7-yn-2-yl)cyclopropanecarboxylate (2.63) (BLA-III-173). Thionyl chloride (16 □L, 0.217 mmol) was added to a solution of **2.56** (31 mg, 0.072 mmol) in MeOH (0.5 mL) at room temperature and stirred for 7 h. Saturated aqueous Na_2CO_3 (1 mL) was added, the MeOH removed under reduced pressure, and CH_2Cl_2 (2 mL) was added to the crude residue. The layers were separated and the aqueous phase was washed with saturated aqueous NaCl (2 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give 25 mg (85%) of **2.63** as a clear, colorless oil: ^{1}H NMR (500 MHz) □ 7.35-7.29 (comp, 5 H), 5.10 (t, J = 7.8 Hz, 1 H), 4.55 (s, 2 H), 4.13 (t, J = 1.8 Hz, 2 H), 3.74 (s, 3 H), 3.74 (s, 3 H), 3.62 (s, 3 H), 2.88 (app dt, J = 4.5, 2.1 Hz, 2 H), 2.84 (br d, J = 7.8 Hz, 2H), 1.91-1.79 (m, 2 H), 1.66 (s, 3H), 1.35 (app dt, J = 7.2, 5.4 Hz, 1 H), 1.05 (ddd, J =

8.4, 8.1, 4.8 Hz, 1 H); ^{13}C NMR (125 MHz) δ 171.8, 170.5, 170.4, 137.6, 134.9, 128.4, 128.1, 127.8, 120.9, 82.0, 78.9, 71.2, 57.4, 57.1, 52.8, 51.6, 30.8, 29.3, 22.8, 19.7, 17.3, 11.5; IR ($CDCl_3$) 3690, 2954, 2254, 1734, 1602, 1438, 1292, 1201, 1070 cm^{-1}; mass spectrum (CI) *m/z* 443.2074 [$C_{25}H_{31}O_7$ (M+1) requires 443.2070] 443 (base), 411, 335, 153.

NMR Assignments: ^{1}H NMR (500 MHz) δ 7.35-7.29 (comp, 5 H, C19-C20-C21-H), 5.10 (t, *J* = 7.8 Hz, 1 H, C6-H), 4.55 (s, 2 H, C17-H), 4.13 (t, *J* = 1.8 Hz, 2 H, C12-H), 3.74 (s, 3 H, C16-H), 3.74 (s, 3 H, C16-H), 3.62 (s, 3 H, C14-H), 2.88 (app dt, *J* = 4.5, 2.1 Hz, 2 H, C9-H), 2.84 (br d, *J* = 7.8 Hz, 2H, C7-H), 1.91-1.79 (m, 2 H, C2-C4-H), 1.66 (s, 3H, C13-H), 1.35 (app dt, *J* = 7.2, 5.4 Hz, 1 H, C3-H), 1.05 (ddd, *J* = 8.4, 8.1, 4.8 Hz, 1 H, C3-H); ^{13}C NMR (125 MHz) δ 171.8 (C1), 170.5 (C14), 170.4 (C14), 137.6 (C18), 134.9 (C5), 128.4 (C20), 128.1 (C21), 127.8 (C19), 120.9 (C6), 82.0 (C11), 78.9 (C10), 71.2 (C17), 57.4 (C8), 57.1 (C12), 52.8 (C16), 51.6 (C16), 30.8 (C7), 29.3 (C2), 22.8 (C9), 19.7 (C4), 17.3 (C13), 11.5 (C3).

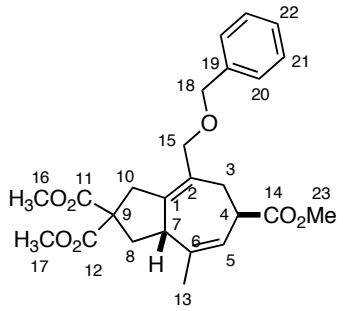


2.64

(3a*S*,4*Z*,6*R*,8*E*)-dimethyl 8-(benzyloxymethyl)-6-(hydroxymethyl)-4-methyl-3,3a,6,7-tetrahydroazulene-2,2(1*H*)-dicarboxylate (2.64) (BLA-III-177).

$[Rh(CO)_2Cl]_2$ (1 mg, 1.2 μmol) was dissolved in degassed toluene (0.5 mL), stirred at room temperature for 5-10 min, and then a solution of **2.62** (5 mg, 0.012 mmol) in degassed toluene (1 mL) was added at room temperature over 10 sec. The resulting solution was heated 110 °C (bath temperature), with stirring for an additional 5 h. The reaction was then allowed to cool to room temperature, and filtered through a short column of neutral alumina. The filtrate was concentrated under reduced pressure, and the crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 4 mg (80%) of **2.64** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.35-7.27 (comp, 5 H), 5.34 (br s, 1 H), 4.45 (s, 2 H), 4.06 (d, *J* = 11.6 Hz, 1 H), 4.03 (d, *J* = 11.4 Hz, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.64-3.57 (m, 1 H), 3.51-3.46 (m, 1 H), 3.18 (dd, *J* = 17.1, 1.8 Hz, 1 H), 2.84 (br d, *J* = 15.3 Hz, 1 H), 2.78 (ddd, *J* = 12.7, 7.8, 2.2 Hz, 1 H), 2.31-2.26 (m, 1 H), 2.07 (t, *J* = 12.4 Hz, 1 H), 1.76 (s, 3 H).

NMR Assignments: ^{1}H NMR (500 MHz) δ 7.35-7.27 (comp, 5 H, C20-C21-C22-H), 5.34 (br s, 1 H, C5-H), 4.45 (s, 2 H, C18-H), 4.06 (d, *J* = 11.6 Hz, 1 H, C15-H), 4.03 (d, *J* = 11.4 Hz, 1 H, C15-H), 3.74 (s, 3 H, C16-H), 3.73 (s, 3 H, C17-H), 3.64-3.57 (m, 1 H, C7-H), 3.51-3.46 (m, 1 H, C14-H), 3.18 (dd, *J* = 17.1, 1.8 Hz, 1 H, C10-H), 2.84 (br d, *J* = 15.3 Hz, 1 H, C10-H), 2.78 (ddd, *J* = 12.7, 7.8, 2.2 Hz, 1 H, C8-H), 2.31-2.26 (m, 1 H, C3-C4-H), 2.07 (t, *J* = 12.4 Hz, 1 H, C8-H), 1.76 (s, 3 H, C13-H).

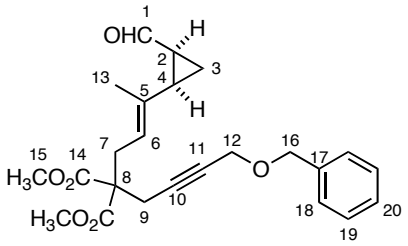


2.65

(3a*S*,4*Z*,6*R*,8*E*)-trimethyl 8-(benzyloxymethyl)-4-methyl-3,3a,6,7-tetrahydroazulene-2,2,6(1*H*)-tricarboxylate (2.65) BLA-III-177. $[Rh(CO)_2Cl]_2$ (1 mg, 2.3 μmol) was added in one portion to a solution of **2.63** (10 mg, 0.022 mmol) in degassed toluene (0.5 mL). The solution was stirred at room temperature for 15 min and then at 110 ˚C (bath temperature) for 5 h. The reaction was then allowed to cool to room temperature and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 5 mg (50%) of **2.65** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.35-7.32 (comp, 5 H), 5.54 (app ddt, *J* = 2.6, 2.4, 1.2 Hz 1 H), 4.46-4.44 (comp, 2 H), 4.04 (br s, 2 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.70 (s, 3 H), 3.62-3.60 (m, 1 H), 3.16 (br d, *J* = 16.7 Hz, 1 H), 3.17-3.13 (m, 1 H), 2.82 (br d, *J* = 16.5 Hz, 1 H), 2.78 (ddd, *J* = 12.6, 7.8, 2.2 Hz 1 H), 2.62-2.53 (m, 2 H), 2.07 (t, *J* = 12.2 Hz, 1 H), 1.77 (dd, *J* = 2.4, 1.4 Hz, 3 H); ^{13}C NMR (125 MHz) δ 174.8, 171.7, 171.5, 140.8, 138.5, 135.6, 129.8, 128.4, 127.7, 127.6, 123.6, 71.8, 71.1, 57.6, 52.8, 51.9, 51.9, 44.2, 39.3, 38.4, 30.9, 24.9; mass spectrum (CI) *m/z* 441.1913 [$C_{25}H_{29}O_7$ (M+1) requires 441.1913] 443, 411, 335 (base), 303, 275.

NMR Assignments: ^{1}H NMR (500 MHz) δ 7.35-7.32 (comp, 5 H, C20-C21-C22-H), 5.54 (app ddt, *J* = 2.6, 2.4, 1.2 Hz 1 H, C5-H), 4.46-4.44 (comp, 2 H, C15-H), 4.04 (br s, 2 H, C18-H), 3.74 (s, 3 H, C16-H), 3.73 (s, 3 H, C17-H), 3.70 (s, 3 H, C23-H),

3.62-3.60 (m, 1 H, C7-H), 3.16 (br d, *J* = 16.7 Hz, 1 H, C10-H), 3.17-3.13 (m, 1 H, C4-H), 2.82 (br d, *J* = 16.5 Hz, 1 H, C10-H), 2.78 (ddd, *J* = 12.6, 7.8, 2.2 Hz 1 H, C8-H), 2.62-2.53 (m, 2 H, C3-H), 2.07 (t, *J* = 12.2 Hz, 1 H, C8-H), 1.77 (dd, *J* = 2.4, 1.4 Hz, 3 H, C13-H); ^{13}C NMR (125 MHz) 174.8 (C14), 171.7 (C11), 171.5 (C12), 140.8 (C1), 138.5 (C19), 135.6 (C6), 129.8 (C2), 128.4 (C22), 127.7 (C21), 127.6 (C20), 123.6 (C5), 71.8 (C18), 71.1 (C15), 57.6 (C9), 52.8 (C23), 51.9 (C16), 51.9 (C17), 44.2 (C7), 39.3 (C4), 38.4 (C8), 30.9 (C4), 24.9 (C13).



2.68

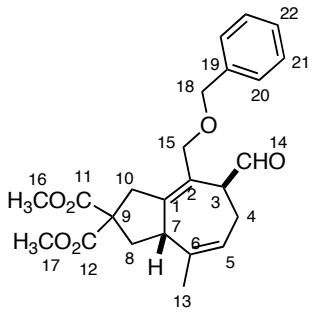
2-(4-Benzyloxybut-2-ynyl)-2-[3-(2*S*,4*S*)-(2-formylcyclopropyl)but-2-enyl]-malonic acid dimethyl ester (2.68) (BLA-III-274). Oxalyl chloride (50 L, 0.485 mmol) was added dropwise to a solution of **2.56** (104 mg, 0.242 mmol) and DMF (5 drops) in CH_2Cl_2 (2.5 mL) at 0 ˚C. The reaction was allowed to warm to room temperature by removal of the cooling bath and then stirred for 3 h. The mixture was concentrated under reduced pressure, and the crude acid chloride was dissolved in THF (2 mL). The solution was cooled to –78 ˚C, and a slurry of $LiAlH(O^tBu)_3$ (124 mg, 0.485 mmol) in THF (0.5 mL) was added. The reaction was stirred at –78 ˚C for 1 h. Aqueous 1M HCl (2 mL) was added, and the mixture allowed to warm to room temperature by removal of the cooling bath, and then the layers were separated. The aqueous phase was extracted with EtOAc (3 x 2 mL), and the combined organic fractions were then dried

(Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 84 mg (84%) of **2.68** as a clear, colorless oil.

Oxidation of alcohol 2.62 (BLA-III-243). Dess-Martin periodinane (58 mg, 0.137 mmol) was added in one portion to a solution of **2.62** (104 mg, 0.242 mmol) in CH_2Cl_2 (1 mL) at room temperature, and the mixture was stirred for 1.5 h. Saturated aqueous $NaHCO_3/Na_2S_2O_3$ (1 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 1 mL), and the combined organic fractions were then dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 19 mg (100%) of **2.68** as a clear, colorless oil: ^{1}H NMR (300 MHz) □ 8.74 (d, *J* = 6.9 Hz, 1 H), 7.36-7.28 (comp, 5 H), 5.31 (t, *J* = 7.8 Hz, 1 H), 4.55 (s, 2 H), 4.13 (t, *J* = 2.1 Hz, 2 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 2.91-2.83 (comp, 4 H), 2.11 (app dt, *J* = 15.9, 8.1 Hz, 1 H), 1.86 (app ddt, *J* = 12.0, 7.8, 4.8 Hz, 1 H), 1.72 (s, 3H), 1.59 (app dt, *J* = 7.2, 5.1 Hz, 1 H), 1.33 (app dt, *J* = 7.8, 5.4 Hz, 1 H); ^{13}C NMR (75 MHz) □ 201.7, 170.3, 137.5, 134.9, 128.1, 127.8, 121.1, 81.3, 79.3, 71.2, 57.3, 56.9, 52.8, 30.6, 30.2, 28.3, 23.2, 17.8, 11.8; IR ($CDCl_3$) 2953, 2853, 2256, 1736, 1697, 1437, 1292, 1208, 1069 cm^{-1}; mass spectrum (CI) *m/z* 413.1959 [$C_{24}H_{29}O_6$ (M+1) requires 413.1964] 413 (base), 305, 245.

NMR Assignments: ^{1}H NMR (300 MHz) □ 8.74 (d, *J* = 6.9 Hz, 1 H, C1-H), 7.36-7.28 (comp, 5 H, C18-C19-C20-H), 5.31 (t, *J* = 7.8 Hz, 1 H, C6-H), 4.55 (s, 2 H, C16-H), 4.13 (t, *J* = 2.1 Hz, 2 H, C12-H), 3.74 (s, 3 H, C15-H), 3.73 (s, 3 H, C15-H), 2.91-2.83 (comp, 4 H, C7-C9-H), 2.11 (app dt, *J* = 15.9, 8.1 Hz, 1 H, C2-H), 1.86 (app ddt, *J* = 12.0, 7.8, 4.8 Hz, 1 H, C4-H), 1.72 (s, 3H, C13-H), 1.59 (app dt, *J* = 7.2, 5.1 Hz, 1 H, C3-H), 1.33 (app dt, *J* = 7.8, 5.4 Hz, 1 H, C3-H); ^{13}C NMR (75 MHz) □ 201.7 (C1), 170.3 (C14), 137.5 (C5), 134.9 (C17), 128.1 (C_{AR}), 127.8 (C_{AR}), 121.1 (C6), 81.3 (C10), 79.3

(C11), 71.2 (C16), 57.3 (C12), 56.9 (C15), 52.8 (C8), 30.6 (C7), 30.2 (C2), 28.3 (C4), 23.2 (C9), 17.8 (C13), 11.8 (C3).

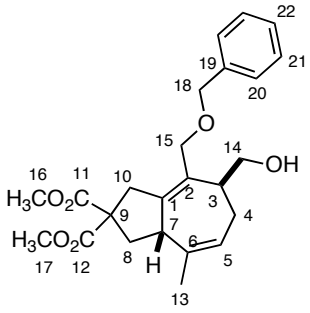


2.69

(3a*S*,7*S*)-8-Benzyloxymethyl-7-formyl-4-methyl-3,3a,6,7-tetrahydro-1*H*-azulene-2,2-dicarboxylic acid dimethyl ester (2.69) (BLA-III-245). $[Rh(CO)_2Cl]_2$ (2 mg, 4.8 μmol) was dissolved in degassed toluene (2 mL), and a solution of **2.68** (20 mg, 0.048 mmol) in degassed toluene (5 mL) was added. The resulting mixture was heated for 30 min at 110 ˚C (bath temperature). The mixture was allowed to cool to room temperature by removal of the oil bath, and then filtered through a short plug of neutral alumina. The filtrate was concentrated under reduced pressure, and the crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 17 mg (85%) of **2.69** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 9.59 (s, 1 H), 7.36-7.27 (comp, 5 H), 5.51-5.49 (m, 1 H), 4.51 (d, *J* = 11.6 Hz, 1 H), 4.46 (d, *J* = 11.8 Hz, 1 H), 4.01 (app dt, *J* = 12.1, 1.2 Hz, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.37 (br s, 1 H), 3.23 (dd, *J* = 17.3, 2.0 Hz, 1 H), 3.20 (t, *J* = 6.0 Hz, 1 H), 2.89 (dd, *J* = 16.7, 1.4 Hz, 1 H), 2.73 (ddd, *J* = 12.4, 7.4, 2.0 Hz, 1 H), 2.68-2.59 (m, 1 H), 2.35-2.29 (m, 1 H), 2.07 (t, *J* = 12.7 Hz, 1 H), 1.68 (d, *J* = 0.6 Hz, 1 H); ^{13}C NMR (125 MHz) δ 200.4, 171.7, 171.4, 142.5, 138.2, 134.3,

128.4, 127.7, 127.6, 122.8, 71.9, 71.2, 57.3, 52.9, 52.8, 51.7, 44.5, 39.3, 39.3, 26.4, 24.2; IR ($CDCl_3$) 3022, 2954, 1732, 1698, 1436, 1374, 1291, 1211, 1071 cm^{-1}; mass spectrum (CI) *m/z* 413.1956 [$C_{24}H_{29}O_6$ (M+1)] 413, 305 (base), 273, 245.

NMR Assignments: ^1H NMR (500 MHz) δ 9.59 (br s, 1 H, C14-H), 7.36-7.27 (comp, 5 H, C18-C19-C20-H), 5.51-5.49 (m, 1 H, C5-H), 4.51 (d, *J* = 11.6 Hz, 1 H, C18-H), 4.46 (d, *J* = 11.8 Hz, 1 H, C18-H), 4.01 (app dt, *J* = 12.1, 1.2 Hz, 1 H, C15-H), 3.76 (s, 3 H, C16-H), 3.74 (s, 3 H, C17-H), 3.37 (br s, 1 H, C7-H), 3.23 (dd, *J* = 17.3, 2.0 Hz, 1 H, C10-H), 3.20 (t, *J* = 6.0 Hz, 1 H, C3-H), 2.89 (dd, *J* = 16.7, 1.4 Hz, 1 H, C10-H), 2.73 (ddd, *J* = 12.4, 7.4, 2.0 Hz, 1 H, C8-H), 2.68-2.59 (m, 1 H, C4-H), 2.35-2.29 (m, 1 H, C4-H), 2.07 (t, *J* = 12.7 Hz, 1 H, C8-H), 1.68 (d, *J* = 0.6 Hz, 1 H, C13-H); ^{13}C NMR (125 MHz) δ 200.4 (C14), 171.7 (C11), 171.4 (C12), 142.5 (C1), 138.2 (C19), 134.3 (C6), 128.4 (C22), 127.7 (C21), 127.6 (C20), 122.8 (C5), 71.9 (C18), 71.2 (C15), 57.3 (C9), 52.9 (C16), 52.8 (C17), 51.7 (C3), 44.5 (C7), 39.3 (10), 39.3 (C8), 26.4 (C4), 24.2 (C13).

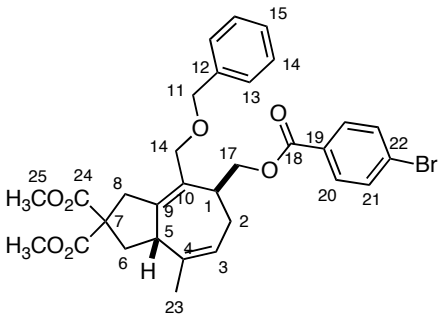


2.70

[2*S*,3*S*]-8-Benzyloxymethyl-7-hydroxymethyl-4-methyl-3,3a,6,7-tetrahydro-1*H*-azulene-2,2-dicarboxylic acid dimethyl ester (2.70) (BLA-III-244). $NaBH_4$ (2 mg, 0.029 mmol) was added in one portion to a solution of **2.69** (6 mg, 0.014 mmol) in THF

(1 mL) at 0 ˚C, and the mixture was stirred for 1 h 15 min. Saturated aqueous NH_4Cl (1 mL) was added and the layers separated. The aqueous phase was extracted with EtOAc (3 x 1 mL), and the combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 5 mg (83%) of **2.70** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.35-7.27 (comp, 5 H), 5.50-5.48 (m, 1 H), 4.53 (s, 2 H), 4.03 (d, *J* = 10.0 Hz, 1 H), 3.79 (d, *J* = 10.0 Hz, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.69 (dd, *J* = 13.9, 5.2 Hz, 1 H), 3.64 (dd, *J* = 10.6, 6.0 Hz, 1 H), 3.60-3.55 (m, 1 H), 3.17 (br d, *J* = 16.7 Hz, 1 H), 2.95-2.92 (m, 1 H), 2.75 (ddd, *J* = 12.4, 7.4, 2.0 Hz, 1 H), 2.42-2.35 (m, 2 H), 2.28-2.20 (comp, 2 H), 2.04 (t, *J* = 12.6 Hz, 1 H), 1.71 (s, 3 H); ^{13}C NMR (125 MHz) δ 171.9, 171.7, 141.8, 137.9, 135.2, 130.7, 128.4, 127.8, 127.7, 123.2, 72.7, 72.2, 64.1, 57.0, 52.9, 52.8, 45.2, 42.9, 39.4, 39.2, 29.0, 23.8; IR ($CHCl_3$) 3468, 3015, 2954, 1731, 1436, 1273, 1201, 1060 cm^{-1}; mass spectrum (CI) *m/z* 415.2124 [$C_{25}H_{31}O_6$ (M+1) requires 415.2121] 415, 307 (base), 207, 247.

NMR Assignments: ^{1}H NMR (500 MHz) δ 7.35-7.27 (comp, 5 H, C20-C21-C22-H), 5.50-5.48 (m, 1 H, C5-H), 4.53 (s, 2 H, C18-H), 4.03 (d, *J* = 10.0 Hz, 1 H, C15-H), 3.79 (d, *J* = 10.0 Hz, 1 H, C15-H), 3.74 (s, 3 H, C16-H), 3.73 (s, 3 H, C17-H), 3.69 (dd, *J* = 13.9, 5.2 Hz, 1 H, C14-H), 3.64 (dd, *J* = 10.6, 6.0 Hz, 1 H, C14-H), 3.60-3.55 (m, 1 H, C7-H), 3.17 (br d, *J* = 16.7 Hz, 1 H, C10-H), 2.95-2.92 (m, 1 H, C10-H), 2.75 (ddd, *J* = 12.4, 7.4, 2.0 Hz, 1 H, C8-H), 2.42-2.35 (m, 2 H, C3-C4-H), 2.28-2.20 (comp, 2 H, C4-H), 2.04 (t, *J* = 12.6 Hz, 1 H, C8-H), 1.71 (s, 3 H, C13-H); ^{13}C NMR (125 MHz) δ 171.9 (C11), 171.7 (C12), 141.8 (C1), 137.9 (C19), 135.2 (C6), 130.7 (C2), 128.4 (C22), 127.8 (C21), 127.7 (C20), 123.2 (C5), 72.7 (C18), 72.2 (C15), 64.1 (C14), 57.0 (C9), 52.9 (C16), 52.8 (C17), 45.2 (C7), 42.9 (C3), 39.4 (C10), 39.2 (C8), 29.0 (C4), 23.8 (C13).

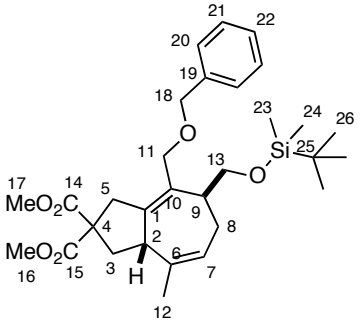


2.71

[2*S*,3*S*]-8-Benzyloxymethyl-7-(4-bromobenzoyloxymethyl)-4-methyl-3,3a,6,7-tetrahydro-1*H*-azulene-2,2-dicarboxylic acid dimethyl ester (2.71) (BLA-IV-287). 4-Bromobenzoyl chloride (16 mL, 0.073 mmol) was added in one portion to a stirred solution of **2.70** (15 mg, 0.036 mmol), DMAP (1 mg, 7.3 mol), and pyridine (6.0 L, 0.073 mmol) in CH_2Cl_2 (1 mL) at room temperature, and the reaction was stirred for 4 h. The mixture was then diluted with saturated aqueous NaCl (1 mL) and Et_2O (2 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 2 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ (2 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (5:1) to give 17 mg (78%) of **3.64** as an clear, colorless oil: ^{1}H NMR (400 MHz) 7.84 (dt, *J* = 8.8, 2.4 Hz, 2 H), 7.54 (dt, *J* = 8.8, 2.4 Hz, 2 H), 7.33-7.26 (comp m, 5 H), 5.45 (br t, *J* = 5.6 Hz, 1 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 4.44 (d, *J* = 12.0 Hz, 1 H), 4.40 (d, *J* = 7.2 Hz, 2 H), 4.01 (s, 2 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 3.55-3.49 (m, 1 H), 3.15 (d, *J* = 16.8 Hz, 1 H), 2.93 (dd, *J* = 16.8, 2.0 Hz, 1 H), 2.88 (app dq, *J* = 12.0, 7.2, 7.2, 7.2 Hz, 1 H), 2.78 (ddd, *J* = 12.4, 7.2, 2.0 Hz, 1 H), 2.39 (br s, 2 H), 2.05 (t, *J* = 12.4 Hz, 1 H), 1.74 (s, 3 H); IR ($CDCl_3$) 3691, 2954, 2360, 2254, 1792, 1731, 1591, 1436, 1272, 1211, 1172, 1103, 1070, 1043, 1012 cm^{-1}; mass

spectrum (CI) *m/z* 599.1483 [$C_{31}H_{34}O_7Br$ (M+2) requires 599.1467] 627, 599, 597, 595, 505, 491, 489 (base), 384, 379, 365.

NMR Assignments: ^{1}H NMR (400 MHz) 7.84 (dt, *J* = 8.8, 2.4 Hz, 2 H, C20-H), 7.54 (dt, *J* = 8.8, 2.4 Hz, 2 H, C21-H), 7.33-7.26 (comp m, 5 H, C14-C15-C16-H), 5.45 (br t, *J* = 5.6 Hz, 1 H, C3-H), 4.49 (d, *J* = 12.0 Hz, 1 H, C12-H), 4.44 (d, *J* = 12.0 Hz, 1 H, C12-H), 4.40 (d, *J* = 7.2 Hz, 2 H, C17-H), 4.01 (s, 2 H, C11-H), 3.73 (s, 3 H, C25-H), 3.72 (s, 3 H, C25-H), 3.55-3.49 (m, 1 H, C1-H), 3.15 (d, *J* = 16.8 Hz, 1 H, C8-H), 2.93 (dd, *J* = 16.8, 2.0 Hz, 1 H, C8-H), 2.88 (app dq, *J* = 12.0, 7.2, 7.2, 7.2 Hz, 1 H, C5-H), 2.78 (ddd, *J* = 12.4, 7.2, 2.0 Hz, 1 H, C6-H), 2.39 (br s, 2 H, C2-H), 2.05 (t, *J* = 12.4 Hz, 1 H, C6-H), 1.74 (s, 3 H, C23-H).

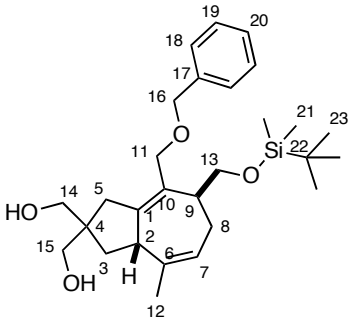


2.72

(3a*S*,4*Z*,7*S*,8*E*)-dimethyl 8-((benzyloxy)methyl)-3,3a,6,7-tetrahydro-7-((*t*-butyl dimethylsiloxy)methyl)-4-methylazulene-2,2(1*H*)-dicarboxylate (2.72) (BLA-VI-268). TBSCl (24 mg, 0.16 mmol) was added in one portion to a solution of imidazole (11 mg, 0.16 mmol) and **2.70** (32 mg, 78.0 mol) in DMF (2 mL) at room temperature, and the reaction was stirred for 4 h. Saturated aqueous NaCl (1 mL) was added, and the

layers were separated. The aqueous phase was extracted with Et_2O (3 x 1 mL), and the combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexane/EtOAc (2:1) to provide 33 mg (81%) of **2.72** as a clear, colorless oil: ^{1}H NMR (500 MHz) □ 7.32-7.31 (comp, 5 H), 5.42-5.41 (m, 1 H), 4.47 (d, *J* = 12.0 Hz, 1 H), 4.42 (d, *J* = 12.0 Hz, 1 H), 3.96 (d, *J* = Hz, 1 H), 3.95 (d, *J* = Hz, 1 H), 3.72 (s, 3 H), 3.71 (s, 3 H), 3.64 (app t, *J* = 9.5 Hz, 1 H), 3.59 (dd, *J* = 9.5, 5.5 Hz, 1 H), 3.37-3.36 (m, 1 H), 3.10 (d, *J* = 17.0 Hz, 1 H), 2.96 (dd, *J* = 17.5, 2.5 Hz, 1 H), 2.54 (m, 1 H), 2.35-2.31 (m, 1 H), 2.27-2.23 (m, 1 H), 1.96 (app t, *J* = 13.0 Hz, 1 H), 1.70 (d, *J* = 1.0 Hz, 3 H), 0.84 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (125 MHz) □ 171.9, 171.9, 138.8, 138.4, 133.2, 131.9, 128.3, 127.6, 127.4, 123.4, 72.4, 71.8, 62.6, 57.4, 56.7, 52.7, 46.5, 41.7, 39.1, 25.8, 25.6, 17.9, –3.7; mass spectrum (CI) *m/z* 529.2957 [$C_{30}H_{45}O_6Si$ (M+1) requires 529.2985] 529, 421, 289 (base), 275.

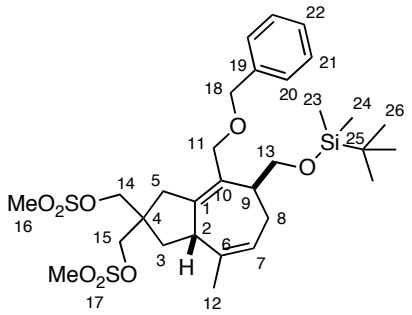
NMR Assignments: ^{1}H NMR (400 MHz) □ 7.32-7.31 (comp, 5 H, C20-C21-C22 -H), 5.42-5.41 (m, 1 H, C7-H), 4.47 (d, *J* = 12.0 Hz, 1 H, C18-H), 4.42 (d, *J* = 12.0 Hz, 1 H, C18-H), 3.96 (d, *J* = Hz, 1 H, C11-H), 3.95 (d, *J* = Hz, 1 H, C11-H), 3.72 (s, 3 H, C16-H), 3.71 (s, 3 H, C17-H), 3.64 (app t, *J* = 9.5 Hz, 1 H, C13-H), 3.59 (dd, *J* = 9.5, 5.5 Hz, 1 H, C13-H), 3.37-3.36 (m, 1 H, C9-H), 3.10 (d, *J* = 17.0 Hz, 1 H, C5-H), 2.96 (dd, *J* = 17.5, 2.5 Hz, 1 H, C5-H), 2.54 (m, 1 H, C5-H), 2.35-2.31 (m, 1 H, C2-H), 2.27-2.23 (m, 1 H, C3-H), 1.96 (app t, *J* = 13.0 Hz, 1 H, C3-H), 1.70 (d, *J* = 1.0 Hz, 3 H, C12-H), 0.84 (s, 9 H, C30-C31-C32-H), 0.03 (s, 6 H, C28-C29-H); ^{13}C NMR (125 MHz) □ 171.9 (C14), 171.9 (C15), 138.8 (C6), 138.4 (C19), 133.2, 131.9, 128.3, 127.6, 127.4, 123.4 (C7), 72.4 (C18), 71.8 (C11), 62.6 (C13), 57.4, 56.7, 52.7 (C16,C17), 46.5, 41.7, 39.1, 25.8 (C12), 25.6 (C26), 17.9 (C25), –3.7 (C23,C24).



2.73

(3a*S*,4*Z*,7*S*,8*E*)-Dimethyl 8-((benzyloxy)methyl)-3,3a,6,7-tetrahydro-7-((*t*-butyl dimethylsiloxy)methyl)-4-methylazulene-2,2(1*H*)-diol (2.73) (BLA-VII-272). $LiAlH_4$ (21 mg, 0.55 mmol) was added to a stirred solution of diester **2.72** (145 mg, 0.27 mmol) in THF (3 mL) at 0 ˚C. The reaction was allowed to warm slowly to room temperature and stirred for 4 h. The mixture was then cooled to 0 ˚C, and saturated potassium sodium tartrate (3 mL) was added, and the mixture was stirred for 30 min at room temperature. The layers were separated, and the aqueous phase was extracted with EtOAc (5 x 5 mL). The combined organic fractions were washed with saturated aqueous NaCl (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield 120 mg (91%) of **2.73** as an opaque, colorless oil: ^{1}H NMR (500 MHz) □ 7.34-7.28 (comp, 5 H), 5.42-5.40 (m, 1 H), 4.49 (d, *J* = 11.6 Hz, 1 H), 4.44 (d, *J* = 11.6 Hz, 1 H), 3.97 (d, *J* = 10.4 Hz, 1 H), 3.95 (d, *J* = 10.4 Hz, 1 H), 3.71 (d, *J* = 9.2 Hz, 1 H), 3.65 (d, *J* = 9.2 Hz, 1 H), 3.74-3.57 (comp, 4 H), 3.43-3.38 (m, 1 H), 2.55-2.52 (m, 1 H), 2.41-2.16 (comp, 6 H), 1.71 (s, 3 H), 0.88 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR (125 MHz) □ 141.8, 138.5, 134.8, 131.5, 128.3, 127.8, 127.6, 122.7, 72.8, 72.1, 71.1, 67.4, 62.9, 45.7, 45.3, 44.5, 42.4, 42.2, 37.6, 37.5, 35.9, 18.3, –5.4, –5.4; mass spectrum (CI) *m/z* 473.3063 [$C_{28}H_{45}O_4Si$ (M+1) requires 473.3087] 473, 365, 233, 215 (base).

NMR Assignments: ^{1}H NMR (500 MHz) δ 7.34-7.28 (comp, 5 H, C18-C19-C20-H), 5.42-5.40 (m, 1 H, C7-H), 4.49 (d, *J* = 11.6 Hz, 1 H, C16-H), 4.44 (d, *J* = 11.6 Hz, 1 H, C16-H), 3.97 (d, *J* = 10.4 Hz, 1 H, C11-H), 3.95 (d, *J* = 10.4 Hz, 1 H, C11-H), 3.71 (d, *J* = 9.2 Hz, 1 H, C13-H), 3.65 (d, *J* = 9.2 Hz, 1 H, C13-H), 3.74-3.57 (comp, 4 H, C14-C15-H), 3.43-3.38 (m, 1 H, C2-H), 2.55-2.52 (m, 1 H, C9-H), 2.41-2.16 (comp, 6 H, C3-C5-C8-H), 1.71 (s, 3 H, C12-H), 0.88 (s, 9 H, C23-H), 0.01 (s, 6 H, C21-H); ^{13}C NMR (125 MHz) δ 141.8 (C6), 138.5 (C17), 134.8, 131.5, 128.3, 127.8, 127.6, 122.7 (C6), 72.8 (C16), 72.1 (C11), 71.1 (C14), 67.4 (C15), 62.9 (C13), 45.7 (C2), 45.3 (C4), 44.5 (C5), 42.4 (C9), 42.2 (C3), 37.6 (C8), 37.5 (C12), 35.9 (C23), 18.3 (C22), –5.4 (C21), –5.4 (C21).

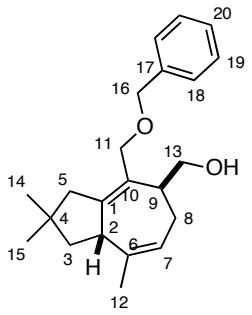


2.74

((3a*S*,4*Z*,7*S*,8*E*)-8-(benzyloxymethyl)-7-((*tert*-butyldimethylsilyloxy)methyl)-4-methyl-2-((methylperoxy)thio)oxy))methyl)-1,2,3,3a,6,7-hexahydroazulen-2-yl)methyl methanesulfonate (2.74) (BLA-VII-277). Methanesulfonyl chloride (291 mg, 0.20 mL, 2.50 mmol) was added dropwise to a stirred solution of **2.73** (120 mg, 0.25 mmol) and Et_3N (257 mg, 0.35 mL, 2.50 mmol) in CH_2Cl_2 (5 mL) at 0 ˚C, and the resultant mixture was stirred for 3 h. Saturated aqueous $NaHCO_3$ (5 mL) was added, and

the layers were separated. The aqueous phase was extracted with Et_2O (3x mL), and the combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 137 mg (79%) of **3.67** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 7.37-7.28 (comp, 5 H), 5.48-5.44 (m, 1 H), 4.49 (d, *J* = 11.6 Hz, 1 H), 4.44 (d, *J* = 11.6 Hz, 1 H), 4.21-4.06 (comp, 2 H), 4.16 (d, *J* = 9.6 Hz, 1 H), 4.08 (d, *J* = 9.6 Hz, 1 H), 3.92 (br s, 1 H), 3.70-3.62 (comp, 2 H), 3.51-3.44 (m, 1 H), 3.03 (s, 3 H), 3.03 (s, 3 H), 2.54-2.53 (m, 1 H), 2.42-2.25 (comp, 3 H), 2.17 (dd, *J* = 13.2, 8.0 Hz, 1 H), 1.70 (s, 3 H), 0.88 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR (125 MHz) δ 138.8, 138.2, 133.9, 133.1, 128.2, 127.6, 127.5, 123.4, 72.5, 72.3, 72.3, 72.1, 69.1, 62.7, 42.8, 37.2, 37.1, 36.6, 36.6, 31.4, 25.8, 24.3, 18.1, –5.1, –5.2; IR ($CDCl_3$) 3100, 3031, 2929, 2856, 2260, 1730, 1469, 1362, 1255, 1178, 1094, 978, 850, 778, 527; mass spectrum (CI) *m/z* 629.2627 [$C_{30}H_{49}O_8SiS_2$ (M+1) requires 629.2638] 629, 557, 555 (base).

NMR Assignments: ^{1}H NMR (500 MHz) δ 7.37-7.28 (comp, 5 H, C20-C21-C22-H), 5.48-5.44 (m, 1 H C7-H), 4.49 (d, *J* = 11.6 Hz, 1 H, C18-H), 4.44 (d, *J* = 11.6 Hz, 1 H, C18-H), 4.21-4.06 (comp, 2 H), 4.16 (d, *J* = 9.6 Hz, 1 H, C11-H), 4.08 (d, *J* = 9.6 Hz, 1 H, C11-H), 3.92 (br s, 1 H, C14-H), 3.70-3.62 (comp, 2 H), 3.51-3.44 (m, 1 H, C13-H), 3.03 (s, 3 H, C16-H), 3.03 (s, 3 H, C17-H), 2.54-2.53 (m, 1 H, C2-H), 2.42-2.25 (comp, 3 H), 2.17 (dd, *J* = 13.2, 8.0 Hz, 1 H), 1.70 (s, 3 H, C12-H), 0.88 (s, 9 H, C25-H), 0.01 (s, 6 H, C23-H); ^{13}C NMR (125 MHz) δ 138.8 (C6), 138.2 (C19), 133.9, 133.1, 128.2, 127.6, 127.5, 123.4 (C7), 72.5 (C18), 72.3 (C14), 72.3 (C15), 72.1 (C11), 69.1 (C13), 62.7 (C2), 42.8 (C4), 37.2, 37.1, 36.6, 36.6, 31.4 (C16,C17), 25.8 (C25), 24.3 (C12), 18.1 (C24), –5.1 (C23), –5.2 (C23).

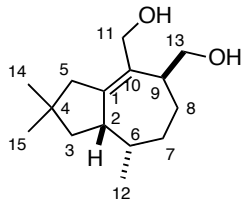


2.75

((3a*E*,5*S*,7*Z*,8a*S*)-4-(benzyloxymethyl)-2,2,8-trimethyl-1,2,3,5,6,8a-hexahydroazulen-5-yl)methanol (2.75) (BLA-VIII-22, BLA-VIII-25). A 1.0 M solution of $LiBHEt_3$ (0.71 mL, 0.71 mmol) in THF was added to a solution of **2.74** (56 mg, 0.08 mmol) in THF (2 mL) at room temperature, and the mixture was stirred for 8 h. The reaction was then cooled to 0 ˚C, 1 M HCl (2 mL) was added, and the mixture allowed to warm to room temperature. The layers were separated, and the aqueous phase was extracted with EtOAc (5 x mL). The combined organic fractions were washed with saturated aqueous NaCl (mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was then dissolved in THF (1.7 mL), and a solution of TBAF (85 mg, 0.27 mmol) in THF (0.3 mL) was added at room temperature. The reaction was stirred for 3 h and then saturated aqueous NaCl (mL) was added, and the layers were separated. The aqueous phase was extracted with EtOAc (5 x mL), the combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 20 mg (70%) of **2.75** as a clear, colorless oil: ^{1}H NMR (500 MHz) □ 7.38-7.27 (comp, 5 H), 5.49-5.44 (m, 1 H), 4.52 (s, 1 H), 4.01 (d, *J* = 9.6 Hz, 1 H), 3.75-3.68 (comp, 3 H), 2.51 (app t, *J* = 6.0 Hz, 1 H), 2.47-2.78 (comp, 2 H), 2.25 (dd, *J* = 16.0, 2.0 Hz, 1 H), 2.20-

2.18 (m, 1 H), 2.13 (d, *J* = 16.0 Hz, 1 H), 1.76 (ddd, *J* = 11.6, 7.6, 2.0 Hz, 1 H), 1.68 (s, 3 H), 1.51 (app t, *J* = 12.0 Hz, 1 H), 1.07 (s 3 H), 0.96 (s, 3 H); ^{13}C NMR (125 MHz) □ 147.2, 138.1, 137.2, 129.2, 128.4, 127.8, 127.7, 122.5, 72.7, 72.5, 64.3, 47.0, 46.0, 44.8, 43.3, 35.4, 29.4, 29.3, 26.8, 23.9; IR ($CDCl_3$) 2955, 2247, 1602, 1454, 1365, 1307, 1058; mass spectrum (CI) *m/z* 325.2171 [$C_{22}H_{29}O_2$ (M+1) requires 325.2168] 327, 323, 295, 247, 219 (base).

NMR Assignments: ^{1}H NMR (500 MHz) □ 7.38-7.27 (comp, 5 H, C18-C19-C20-H), 5.49-5.44 (m, 1 H, C7-H), 4.52 (s, 1 H, C16-H), 4.01 (d, *J* = 9.6 Hz, 1 H, C11-H), 3.75-3.68 (comp, 3 H, C11-C13-H), 2.51 (app t, *J* = 6.0 Hz, 1 H, C2-H), 2.47-2.78 (comp, 2 H, C9-C8-H), 2.25 (dd, *J* = 16.0, 2.0 Hz, 1 H, C5-H), 2.20-2.18 (m, 1 H, C3-H), 2.13 (d, *J* = 16.0 Hz, 1 H, C5-H), 1.76 (ddd, *J* = 11.6, 7.6, 2.0 Hz, 1 H, C8-H), 1.68 (s, 3 H, C12-H), 1.51 (app t, *J* = 12.0 Hz, 1 H, C3-H), 1.07 (s 3 H, C14-H), 0.96 (s, 3 H, C15-H); ^{13}C NMR (125 MHz) □ 147.2 (C6), 138.1 (C17), 137.2, 129.2, 128.4, 127.8, 127.7, 122.5 (C7), 72.7 (C16), 72.5 (C11), 64.3 (C13), 47.0, 46.0, 44.8, 43.3, 35.4 (C9), 29.4 (C14), 29.3 (C15), 26.8 (C8), 23.9 (C12).

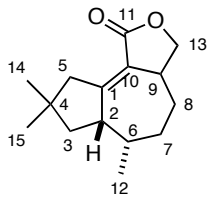


2.4

Tremulenediol A (2.4) (BLA-VIII-95). Palladium on carbon (10 wt%, 1 mg) was added to a solution of **2.75** (5 mg, 15.3 μmol) in MeOH (0.1 mL) at room temperature. The atmosphere in the flask was then replaced with H_2 (1 atm) and the

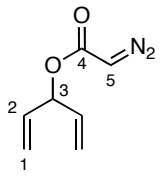
mixture was stirred under and atmosphere of H_2 (balloon) for 3 d. The reaction was then filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to provide 3 mg (82%) of **2.4** as a clear, colorless oil. Spectra results were consistent with literature data:[294] ^{1}H NMR (500 MHz) □ 4.25 (d, *J* = 11.0 Hz, 1 H), 4.02 (app t, *J* = 9.5 Hz, 1 H), 3.84 (dt, *J* = 11.0, 1.5 Hz, 1 H), 3.62 (dd, *J* = 9.5, 5.0 Hz, 1 H), 3.10 (br t, *J* = 8.5 Hz, 1 H), 2.57-2.54 (m, 1 H), 2.29 (dd, *J* = 15.5, 2.5 Hz, 1 H), 1.93 (br d, *J* = 15.0 Hz, 1 H), 1.84-1.81 (m, 1 H), 1.80 (br d, *J* = 11.5 Hz, 1 H), 1.79-1.74 (m, 1 H), 1.61 (dd, *J* = 12.5, 3.0 Hz, 1 H), 1.59-1.58 (m, 1 H), 1.54-1.51 (m, 1 H), 1.38 (br d, *J* = 12.0 Hz, 1 H), 1.07 (s, 3 H), 0.87 (s, 3 H), 0.82 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz) □ 145.8, 132.4, 65.8, 63.3, 48.0, 46.0, 45.5, 45.4, 37.0, 32.6, 31.6, 28.5, 26.9, 22.5, 11.6; IR ($CHCl_3$) 3415, 2929, 2861, 2337, 1601, 1465, 1265, 1016; mass spectrum (CI) *m/z* 238.1910 [$C_{15}H_{26}O_2$ (M+1) requires 238.1932] 237, 221 (base), 203; $[a]_D^{25}$ = +40.0° (*c* 0.24, MeOH).

NMR Assignments: ^{1}H NMR (500 MHz) □ 4.25 (d, *J* = 11.0 Hz, 1 H, C11-H), 4.02 (app t, *J* = 9.5 Hz, 1 H, C12-H), 3.84 (dt, *J* = 11.0, 1.5 Hz, 1 H, C11-H), 3.62 (dd, *J* = 9.5, 5.0 Hz, 1 H, C12-H), 3.10 (br t, *J* = 8.5 Hz, 1 H, C7-H), 2.57-2.54 (m, 1 H, C3-H), 2.29 (dd, *J* = 15.5, 2.5 Hz, 1 H, C10-H), 1.93 (br d, *J* = 15.0 Hz, 1 H, C10-H), 1.84-1.81 (m, 1 H, C5-H), 1.80 (br d, *J* = 11.5 Hz, 1 H, C4-H), 1.79-1.74 (m, 1 H, C6-H), 1.61 (dd, *J* = 12.5, 3.0 Hz, 1 H, C5-H), 1.59-1.58 (m, 1 H, C4-H), 1.54-1.51 (m, 1 H, C8-H), 1.38 (br d, *J* = 12.0 Hz, 1 H, C8-H), 1.07 (s, 3 H, C14-H), 0.87 (s, 3 H, C15-H), 0.82 (d, *J* = 7.0 Hz, 3 H, C13-H); ^{13}C NMR (125 MHz) □ 145.8 (C1), 132.4, (C2), 65.8 (C11), 63.3 (C12), 48.0 (C10), 46.0 (C7), 45.5 (C8), 45.4 (C3), 37.0 (C9), 32.6 (C5), 31.6 (C6), 28.5 (C14), 26.9 (C15), 22.5 (C4), 11.6 (C13).



2.3

Tremulenolide A (2.3) (BLA-VIII-168). MnO_2 (3.0 mg, 33.0 μmol) was added to a solution of **2.4** (4.0 mg, 16.0 μmol) in CH_2Cl_2 (1 mL) at room temperature. The resulting mixture was stirred for 24 h, filtered through a short plug of silica gel and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (5:1) to provide 3.4 mg (86%) of **2.3** as a clear, colorless oil. Spectra results were consistent with literature data.[294]

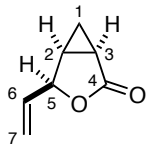


3.6

1,4-Pentadien-3-yl diazoacetate (3.6) (BLA-II-243). *p*-Toluenesulfonylhydrazone of glyoxylic acid chloride (1.4 g, 5.63 mmol) and *N,N*-dimethylamine (0.6 mL, 4.88 mmol) were added to a solution **3.5** (316 mg, 3.76 mmol) in CH_2Cl_2 (19 mL) at 0 ˚C, and the mixture was stirred for 30 min. Et_3N (2.62 mL, 18.78 mmol) was added, the cooling bath was removed, and the reaction was then stirred for 4 h at room temperature. H_2O (20 mL) was added, the aqueous phase was extracted with Et_2O (3 x 20 mL), and the combined organic fractions were washed with saturated aqueous NaCl (100 mL). The combined organic fractions were dried ($MgSO_4$) and

concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with Et_2O/pentane (1:10) to give 396 mg (70%) of **3.6** as a bright, yellow oil. Spectral data was consistent with literature data:[384] ^{1}H NMR (300 MHz) □ 5.84 (comp, 3 H), 5.29 (comp, 4 H), 4.79 (br s, 1 H); mass spectrum (CI) *m/z* 153.0656 [$C_7H_9N_2O_2$ (M+1) requires 153.0664] 149, 125 (base), 110.

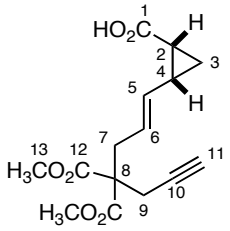
NMR Assignments: ^{1}H NMR (300 MHz) □ 5.84 (comp, 3 H, C2,3-H), 5.29 (comp, 4 H, C1-H), 4.79 (br s, 1 H, C5-H).



3.7

[1S-(1□,5□)]-4-Methyl-4-vinyl-3-oxabicyclo[3.1.0]hexan-2-one (3.7) (BLA-II-251). A solution of **3.6** (379 mg, 2.49 mmol) in CH_2Cl_2 (25 mL) was added to a refluxing solution of Rh_2[5(*R*)-MEPY]$_4$ (46 mg, 50 □mol) in CH_2Cl_2 (100 mL) over 20 h *via* syringe pump. The resulting mixture was then maintained at reflux for an additional 2 hr, cooled to room temperature, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with pentane/Et_2O (1:1) to give 251 mg (81%) of **3.7** as a clear, colorless oil. Spectral data was consistent with literature data:[384] ^{1}H NMR (300 MHz) □ 5.85 (ddd, *J* = 17.1, 10.5, 5.4 Hz, 1 H), 5.39 (dt, *J* = 17.1, 1.2 Hz, 2 H), 5.30 (dt, *J* = 10.8, 1.2 Hz, 2 H), 5.06 (t, *J* = 5.1 Hz, 1 H), 2.29 (dddd, *J* = 9.3, 5.4, 4.5 Hz, 1 H), 2.13 (ddd, *J* = 9.0, 5.7, 3.3 Hz, 1 H), 1.15 (ddd, *J* = 8.7, 7.5, 5.4 Hz, 1 H), 0.95 (m, 1 H); ^{13}C NMR (65 MHz) □ 175.6, 132.8, 118.2, 79.1, 20.9, 18.3, 9.2; mass spectrum (CI) *m/z* 125.0602 [$C_7H_9O_2$ (M+1) requires 125.0602] 172, 149.

NMR Assignments: ^{1}H NMR (300 MHz) δ 5.85 (ddd, *J* = 17.1, 10.5, 5.4 Hz, 1 H, C6-H), 5.39 (dt, *J* = 17.1, 1.2 Hz, 1 H, C7-H), 5.30 (dt, *J* = 10.8, 1.2 Hz, 1 H, C7-H), 5.06 (t, *J* = 5.1 Hz, 1 H, C3-H), 2.29 (dddd, *J* = 9.3, 5.4, 4.5 Hz, 1 H, C1-H), 2.13 (ddd, *J* = 9.0, 5.7, 3.3 Hz, 1 H, C4-H), 1.15 (ddd, *J* = 8.7, 7.5, 5.4 Hz, 1 H, C5-H), 0.95 (m, 1 H, C5-H); ^{13}C NMR (65 MHz) δ 175.6 (C1), 132.8 (C6), 118.2 (C7), 79.1 (C5), 20.9 (C2), 18.3 (C4), 9.2 (C3).



3.9

(1*S*,2*S*,*E*)-2-(4,4-bis(methoxycarbonyl)hept-1-en-6-ynyl)cyclopropanecarboxylic acid (3.9). **Pd(PPh$_3$)$_4$-Catalyzed Allylic Alkylation (BLA-II-297)**. Pd(PPh$_3$)$_4$ (23 mg, 20.2 μmol) was added in one portion to a solution of **3.7** (50 mg, 0.403 mmol) in degassed THF (1 mL) at room temperature. In a separate flask, **3.8** (234 mg, 0.806 mmol) was added to a slurry of sodium hydride (31 mg of a 60% mineral oil suspension, 0.766 mmol) in degassed THF (1 mL) at room temperature, and the resultant mixture was stirred for 20 min. The solution containing the malonate anion was then added *via* cannula to the flask containing **3.7** and Pd(PPh$_3$)$_4$, and the resulting mixture was warmed to 70 ˚C (bath temperature) for 20 h. The resulting dark brown solution was allowed to cool to room temperature and aqueous 1 M HCl (2 mL) added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x

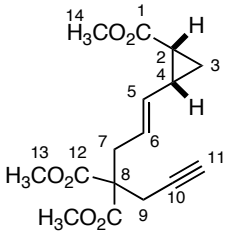
2 mL), and the combined organic fractions were washed with saturated aqueous NaCl (2 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to give 78 mg (84%) of **3.9** as a light brown solid: ^{1}H NMR (500 MHz) □ 5.59 (dd, *J* = 15.0, 9.0 Hz, 1 H), 5.51 (dd, *J* = 15.0, 7.5 Hz, 1 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 2.78 (comp, 4 H), 2.01 (t, *J* = 2.5 Hz, 1 H), 1.96 (m, 1 H), 1.88 (m, 1 H), 1.25 (m, 2 H); ^{13}C NMR (125 MHz) □ 177.7, 170.2, 132.1, 125.5, 78.7, 71.5, 57.1, 52.7, 35.3, 24.6, 22.7, 20.7, 14.9; IR ($CHCl_3$) 3308, 3026, 1733, 1439, 1386, 1294, 1202, 1178, 1076, 974 cm^{-1}; mass spectrum (CI) *m/z* 295.1191 [$C_{16}H_{19}O_5$ (M+1) requires 295.1182] 277, 179.

NMR Assignments: ^{1}H NMR (500 MHz) □ 5.59 (dd, *J* = 15.0, 9.0 Hz, 1 H, C5-H), 5.51 (dd, *J* = 15.0, 7.5 Hz, 1 H, C6-H), 3.74 (s, 3 H, C13-H), 3.72 (s, 3 H, C13-H), 2.78 (comp, 4 H, C7-C9-H), 2.01 (t, *J* = 2.5 Hz, 1 H, C11-H), 1.96 (m, 1 H, C2-H), 1.88 (m, 1 H, C4-H), 1.25 (m, 2 H, C3-H); ^{13}C NMR (125 MHz) □ 177.7 (C1), 170.2 (C12), 132.1 (C5), 125.5 (C6), 78.7 (C10), 71.5 (C11), 57.1 (C8), 52.7 (C13), 35.3 (C7), 24.6 (C3), 22.7 (C9), 20.7 (C2), 14.9 (C4).

$RhCl(PPh_3)_3$/$P(OMe)_3$-Catalyzed Allylic Alkylation (BLA-II-263). $P(OCH_3)_3$ (45 mg, 0.363 mmol) was added to a mixture of $RhCl(PPh_3)_3$ (112 mg, 0.121 mmol) in degassed THF (1 mL), and the mixture was stirred for 10-15 min. The solution was then sonicated for 2 min, and then stirred for an additional 10 min at which time **3.7** (30 mg, 0.242 mmol) was added. The resultant solution was stirred at room temperature for 15 min. In a separate flask, **3.8** (82 mg, 0.484 mmol) was added to a slurry of sodium hydride (19 mg of a 60% mineral oil suspension, 0.460 mmol) in degassed THF (1.5 mL) at room temperature, and the resultant mixture was stirred for 20 min. The solution containing malonate anion was then added *via* cannula to the flask containing **3.7** and $RhCl(PPh_3)_3$/$P(OCH_3)_3$, and the resulting mixture was heated at 40 ˚C (bath temperature)

for 5 h. The resulting dark brown solution was allowed to cool to room temperature, aqueous 1 M HCl (2 mL) was added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 2 mL), and the combined organic fractions were washed with saturated aqueous NaCl (2 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to give 36 mg (49%) of **3.9** as a light brown solid.

$[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation (BLA-III-153). $[Rh(CO)_2Cl]_2$ (6 mg, 0.015 mmol) was dissolved in degassed THF (1 mL) at room temperature and **3.7** (36 mg, 0.29 mmol) added. In a separate flask, **3.8** (99 mg, 0.58 mmol) was added to a slurry of NaH (22 mg of a 60% mineral oil suspension, 0.55 mmol) in degassed THF (1 mL) at room temperature, and the resultant mixture was stirred for 20 min. The solution containing malonate anion was added *via* cannula to the flask containing $[Rh(CO)_2Cl]_2$ and **3.7**, and stirred for 2 h. The resulting dark brown solution was diluted with aqueous 1 M $NaHSO_4$ (2 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic fractions were washed with saturated aqueous NaCl (2 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with $CHCl_3$/MeOH (95:5) to give 45 mg (52%) of **3.9** as a light brown, waxy solid.

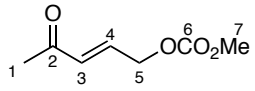


3.9a

2-[3-(2*R*,3*R*)-(2-Methoxycarbonylcyclopropyl)-allyl]-2-prop-2-ynylmalonic acid dimethyl ester (3.9a). (BLA-III-168). $Rh(PPh_3)_3Cl$ (112 mg, 0.121 mmol) was dissolved in degassed THF (1.5 mL) and placed under an atmosphere of CO (1 atm). The solution turned from a brick red to yellow after stirring for 5 min at room temperature. Then **3.7** (30 mg, 0.242 mmol) was added. In a separate flask, **3.8** (82 mg, 0.484 mmol) was added to a slurry of NaH (18 mg of a 60% mineral oil suspension, 0.459 mmol) in degassed THF (1.5 mL) at room temperature, and the resultant mixture was stirred for 20 min. The solution containing malonate anion was added *via* cannula to the flask containing $Rh(PPh_3)_3Cl$ and **3.7**, and the resulting mixture was heated at 40 ˚C (bath temperature) for 24 h. The resulting dark red solution was allowed to cool to room temperature, aqueous 1 M $NaHSO_4$ (3 mL) was added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 3 mL), and the combined organic fractions were washed with brine (3 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was partially purified by flash chromatography eluting with $CHCl_3$/MeOH (95:5). The mixture obtained was dissolved in Et_2O/EtOAc (1:1) (5 mL) and a 1 M solution of CH_2N_2 in Et_2O was added with vigorous stirring until the yellow color persisted (approx. 4 mL). Acetic acid (approx. 4 mL) was added until the yellow color disappeared, and the resulting solution was concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc

(2:1) to give 32 mg (43%) of **3.9a** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 5.54 (ddd, *J* = 15.3, 6.1, 3.1 Hz, 1 H), 5.47 (dd, *J* = 14.7, 7.2 Hz, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.68 (s, 3 H), 2.78-2.76 (comp, 4 H), 2.01 (t, *J* = 2.8 Hz, 1 H), 1.89 (dd, *J* = 8.2, 6.6 Hz, 1 H), 1.88 (ddd, *J* = 10.0, 4.8, 3.8 Hz, 1 H), 1.20 (dd, *J* = 13.5, 4.8 Hz, 1 H) 1.20 (ddd, *J* = 15.3, 11.4, 4.8 Hz, 1 H); ^{13}C NMR (125 MHz) δ 172.2, 170.2, 170.2, 132.6, 125.0, 78.8, 71.4, 57.2, 52.7, 51.7, 35.3, 23.7, 22.6, 20.8, 14.2; IR ($CDCl_3$) 3287, 3007, 2955, 2848, 1765, 1738, 1714, 1462, 1385, 1293, 1199, 1073 cm^{-1}; mass spectrum (CI) *m/z* 309.1343 [$C_{16}H_{21}O_6$ (M+1) requires 309.1338] 309 (base), 277.

NMR Assignments: ^{1}H NMR (500 MHz) δ 5.54 (ddd, *J* = 15.3, 6.1, 3.1 Hz, 1 H, C5-H), 5.47 (dd, *J* = 14.7, 7.2 Hz, 1 H, C6-H), 3.74 (s, 3 H, C13-H), 3.73 (s, 3 H, C13-H), 3.68 (s, 3 H, C14-H), 2.78-2.76 (comp, 4 H, C7-C9-H), 2.01 (t, *J* = 2.8 Hz, 1 H, C11-H), 1.89 (dd, *J* = 8.2, 6.6 Hz, 1 H, C2-H), 1.88 (ddd, *J* = 10.0, 4.8, 3.8 Hz, 1 H, C4-H), 1.20 (dd, *J* = 13.5, 4.8 Hz, 1 H, C3-H) 1.20 (ddd, *J* = 15.3, 11.4, 4.8 Hz, 1 H, C3-H); ^{13}C NMR (125 MHz) δ 172.2 (C1), 170.2 (C12), 170.2 (C12), 132.6 (C5), 125.0 (C6), 78.8 (C10), 71.4 (C11), 57.2 (C8), 52.7 (C13), 51.7 (C14), 35.3 (C9), 23.7 (C2), 22.6 (C7), 20.8 (C4), 14.2 (C3).

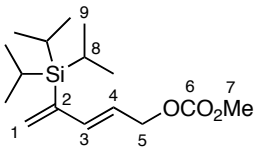


3.25

(*E*)-methyl 4-oxopent-2-enyl carbonate (3.25) (BLA-VIII-90). A steady stream of ozone was bubbled through a solution of **3.24** (1.0 g, 4.9 mmol) in CH_2Cl_2 (50 mL) at –78 ˚C until the blue color of ozone persisted. O_2 was then bubbled through the solution until the blue color dissipated, and PPh_3 (1.9 g, 7.3 mmol) was then added in one portion.

The cooling bath was removed, and the resulting mixture was stirred for 12 h at room temperature. 1-Triphenylphosphranylidene-2-propanone (3.74 mg, 11.7 mmol) was added in one portion, and the reaction was stirred at room temperature for 12 h. The solution was concentrated under reduced pressure, and the crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 570 mg (37%) of **3.25** as a clear, colorless oil: ^{1}H NMR (400 MHz) δ 6.76 (dt, *J* = 16.0, 4.8 Hz, 1 H), 6.30 (dt, *J* = 16.0, 2.0 Hz, 1 H), 4.83 (dd, *J* = 4.8, 2.0 Hz, 1 H), 3.83 (s, 3 H), 2.29 (s, 3 H); ^{13}C NMR (100 MHz) δ 197.2, 154.9, 138.8, 130.6, 65.6, 54.8, 27.1; IR ($CDCl_3$) 3690, 2959, 2256, 1752, 1681, 1445, 1276, 1251, 973 cm^{-1}; mass spectrum (CI) *m/z* 159.0658 [$C_7H_{11}O_4$ (M+1) requires 159.0657] 241, 187, 159 (base), 139, 111.

NMR Assignments: ^{1}H NMR (400 MHz) δ 6.76 (dt, *J* = 16.0, 4.8 Hz, 1 H, C4-H), 6.30 (dt, *J* = 16.0, 2.0 Hz, 1 H, C3-H), 4.83 (dd, *J* = 4.8, 2.0 Hz, 1 H, C5-H), 3.83 (s, 3 H, C7-H), 2.29 (s, 3 H, C1-H); ^{13}C NMR (100 MHz) δ 197.2 (C2), 154.9 (C6), 138.8 (C4), 130.6 (C3), 65.6 (C5), 54.8 (C7), 27.1 (C1).



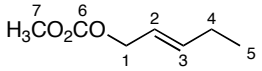
3.14h

(E)-methyl 4-(triisopropylsilyl)penta-2,4-dienyl carbonate (3.14h) (BLA-VIII-93). TIPSOTf (1.36 g, 1.20 mL, 4.40 mmol) was added dropwise to a solution of **3.25** (539 mg, 3.40 mmol) and Et_3N (0.95 mL, 6.80 mmol) in CH_2Cl_2 (12 mL) at 0 ˚C, and the resulting mixture was stirred for 2 h. The solution was diluted with saturated aqueous $NaHCO_3$ (12 mL), and the layers were separated. The aqueous phase was extracted with

CH_2Cl_2 (3 x 12 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (8:1) to provide 930 mg (87%) of **3.14h** as a clear, colorless oil: ^{1}H NMR (400 MHz) δ 6.17-6.07 (comp, 2 H), 4.71 (d, *J* = 4.8 Hz, 2 H), 4.36 (s, 1 H), 4.31 (s, 1 H), 3.79 (s, 3 H), 1.23 (app q, *J* = 6.8 Hz, 3 H), 1.10 (d, *J* = 6.8 Hz, 18 H); ^{13}C NMR (100 MHz) δ 155.4, 154.1, 131.9, 122.9, 95.8, 67.4, 54.5, 17.8, 12.6; IR ($CHCl_3$) 2946, 2867, 1748, 1595, 1443, 1325, 1276, 1028 cm^{-1}; mass spectrum (CI) *m/z* 314.1912 [$C_{16}H_{30}O_4Si$ (M+1) requires 314.1913] 315 (base), 239, 183.

NMR Assignments: ^{1}H NMR (400 MHz) δ 6.17-6.07 (comp, 2 H, C3-C4-H), 4.71 (d, *J* = 4.8 Hz, 2 H, C5-H), 4.36 (s, 1 H, C1-H), 4.31 (s, 1 H, C1-H), 3.79 (s, 3 H, C7-H), 1.23 (app q, *J* = 6.8 Hz, 3 H, C8-H), 1.10 (d, *J* = 6.8 Hz, 18 H, C9-H); ^{13}C NMR (100 MHz) δ 155.4 (C6), 154.1 (C2), 131.9 (C4), 122.9 (C3), 95.8 (C1), 67.4 (C5), 54.5 (C7), 17.8 (C9), 12.6 (C8).

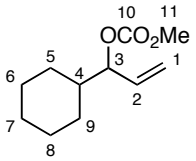
General procedure for the synthesis of allylic methyl carbonates. Methyl chloroformate (284 mg, 0.23 mL, 3.0 mmol) was added to a solution of allylic alcohol (1.0 mmol) and pyridine (237 mg, 0.24 mL, 3.0 mmol) in CH_2Cl_2 (5 mL) at 0 ˚C. The cooling bath was removed, and the mixture was stirred for the indicated time at room temperature. The solution was then diluted with saturated aqueous NaCl (5 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL), and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (ratios given) to provide the desired allylic carbonate.



3.14a

***trans*-Carbonic acid methyl ester pent-2-enyl ester (3.14a) (BLA-III-283)**. Carbonate **3.14a** was obtained in 100% yield (11.6 mmol scale) after 3 h at room temperature as a clear, colorless oil: ^{1}H NMR (400 MHz) □ 5.86 (dddt, *J* = 15.2, 6.0, 5.2, 1.2 Hz, 1 H), 5.57 (dtt, *J* = 15.2, 6.4, 1.6 Hz, 1 H), 4.57 (dd, *J* = 6.8, 0.8 Hz, 2 H), 3.78 (s, 3 H), 2.12-2.04 (comp, 2 H), 1.00 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz) □ 155.2, 138.4, 121.9, 68.4, 54.4, 25.1, 12.9; IR ($CDCl_3$) 3052, 2985, 2304, 1749, 1442, 1421, 1273 cm^{-1}; mass spectrum (CI) *m/z* 145.0868 [$C_7H_{13}O_3$ (M+1) requires 145.0865] 145, 117 (base).

NMR Assignments: ^{1}H NMR (400 MHz) □ 5.86 (dddt, *J* = 15.2, 6.0, 5.2, 1.2 Hz, 1 H, C2-H), 5.57 (dtt, *J* = 15.2, 6.4, 1.6 Hz, 1 H, C3-H), 4.57 (dd, *J* = 6.8, 0.8 Hz, 2 H, C1-H), 3.78 (s, 3 H, C7-H), 2.12-2.04 (comp, 2 H, C4-H), 1.00 (t, *J* = 7.6 Hz, 3 H, C5-H); ^{13}C NMR (100 MHz) □ 155.2 (C6), 138.4 (C2), 121.9 (C3), 68.4 (C7), 54.4 (C1), 25.1 (C4), 12.9 (C5).

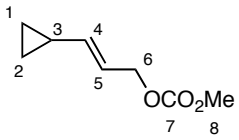


3.14d

Carbonic acid 1-cyclohexylallyl ester methyl ester (3.14d). (BLA-VI-62). Carbonate **3.14d** was obtained in 50% yield (3.56 mmol scale) after 30 min at room

temperature as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1): ^{1}H NMR (400 MHz) δ 5.77 (dddd, *J* = 17.2, 10.4, 7.2, 1.2 Hz, 1 H), 5.27 (dd, *J* = 17.2, 0.8 Hz, 1 H), 5.23 (dd, *J* = 10.4, 0.8 Hz, 1 H), 4.85 (app t, *J* = 2.8 Hz, 1 H), 3.76 (d, *J* = 1.2 Hz, 3 H), 1.81-1.54 (comp, 6 H), 1.28-0.96 (comp, 5 H); ^{13}C NMR (100 MHz) δ 155.3, 134.5, 118.1, 83.2, 54.4, 41.3, 28.3, 28.2, 26.2, 25.8, 25.7; IR ($CHCl_3$) 3022, 2932, 2855, 1744, 1443, 1274, 958, 909 cm^{-1}; mass spectrum (CI) *m/z* 199.1334 [$C_{11}H_{19}O_3$ (M+1) requires 199.1334] 199, 123 (base).

NMR Assignments: ^{1}H NMR (400 MHz) δ 5.77 (dddd, *J* = 17.2, 10.4, 7.2, 1.2 Hz, 1 H, C2-H), 5.27 (dd, *J* = 17.2, 0.8 Hz, 1 H, C1-H), 5.23 (dd, *J* = 10.4, 0.8 Hz, 1 H, C1-H), 4.85 (app t, *J* = 2.8 Hz, 1 H, C3-H), 3.76 (d, *J* = 1.2 Hz, 3 H, C11-H), 1.81-1.54 (comp, 6 H), 1.28-0.96 (comp, 5 H); ^{13}C NMR (100 MHz) δ 155.3 (C10), 134.5 (C2), 118.1 (C1), 83.2 (C3), 54.4 (C11), 41.3 (C4), 28.3, 28.2, 26.2, 25.8, 25.7.

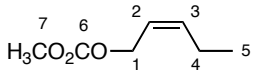


3.14g

Carbonic acid 3-cyclopropylallyl ester methyl ester (3.14g). (BLA-V-96). Carbonate **3.14g** was obtained in 87% yield (3.84 mmol scale) after 3 h at room temperature as a clear, colorless oil after chromatography (pentane/Et_2O = 10:1): ^{1}H NMR (400 MHz) δ 5.67 (dt, *J* = 15.4, 6.8 Hz, 1 H), 5.33 (dd, *J* = 15.4, 8.9 Hz, 1 H), 4.55 (dd, *J* = 6.8, 1.0 Hz, 1 H), 3.77 (s, 3 H), 1.46-1.38 (m, 1 H), 0.75 (app ddt, *J* = 8.0, 6.4, 4.4, 4.4 Hz, 1 H), 0.41 (app ddt, *J* = 9.2, 6.4, 4.4, 4.4 Hz, 1 H); ^{13}C NMR (100 MHz) δ 155.6, 141.4, 120.5, 68.5, 54.5, 13.4, 6.8; IR ($CDCl_3$) 3009, 2958, 2258, 1745, 1444,

1266 cm^{-1}; mass spectrum (CI) *m/z* 156.0788 [$C_8H_{12}O_3$ (M) requires 156.0786] 157, 81 (base).

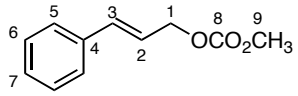
NMR Assignments: ^{1}H NMR (400 MHz) □ 5.67 (dt, *J* = 15.4, 6.8 Hz, 1 H, C5-H), 5.33 (dd, *J* = 15.4, 8.9 Hz, 1 H, C4-H), 4.55 (dd, *J* = 6.8, 1.0 Hz, 1 H, C6-H), 3.77 (s, 3 H, C8-H), 1.46-1.38 (m, 1 H, C3-H), 0.75 (app ddt, *J* = 8.0, 6.4, 4.4, 4.4 Hz, 1 H, C1-H), 0.41 (app ddt, *J* = 9.2, 6.4, 4.4, 4.4 Hz, 1 H, C2-H); ^{13}C NMR (100 MHz) □ 155.6 (C7), 141.4 (C4), 120.5 (C5), 68.5 (C6), 54.5 (C8), 13.4 (C3), 6.8 (C1,2).



3.14e

***cis*-Carbonic acid methyl ester pent-2-enyl ester (3.14e) BLA-III-284**. Carbonate **3.14e** was obtained in 100% yield (5.8 mmol scale) after 3 h at room temperature as a clear, yellow oil: ^{1}H NMR (400 MHz) □ 5.67 (dddd, *J* = 10.4, 7.2, 6.0, 1.6 Hz, 1 H), 5.52 (dddd, *J* = 10.8, 7.2, 5.2, 1.6 Hz, 1 H), 4.68 (dd, *J* = 6.8, 0.8 Hz, 2 H), 3.78 (s, 3 H), 2.17-2.09 (m, 2 H), 1.00 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz) □ 155.4, 137.2, 121.8, 63.4, 54.5, 20.8, 13.9; IR ($CDCl_3$) 3051, 2982, 2304, 1753, 1441, 1360, 1262 cm^{-1}; mass spectrum (CI) *m/z* 145.0862 [$C_7H_{13}O_3$ (M+1) requires 145.0865] 145, 117, 105, 80, 77 (base).

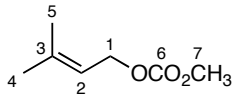
NMR Assignments: ^{1}H NMR (400 MHz) □ 5.67 (dddd, *J* = 10.4, 7.2, 6.0, 1.6 Hz, 1 H, C2-H), 5.52 (dddd, *J* = 10.8, 7.2, 5.2, 1.6 Hz, 1 H, C3-H), 4.68 (dd, *J* = 6.8, 0.8 Hz, 2 H, C1-H), 3.78 (s, 3 H, C7-H), 2.17-2.09 (m, 2 H, C4-H), 1.00 (t, *J* = 7.6 Hz, 3 H, C5-H); ^{13}C NMR (100 MHz) □ 155.4 (C6), 137.2 (C2), 121.8 (C3), 63.4 (C7), 54.5 (C1), 20.8 (C4), 13.9 (C5).



3.14f

***trans*-Carbonic acid methyl ester 3-phenylallyl ester (3.14f) BLA-III-297**. Carbonate **3.14f** was obtained in 100% yield (3.73 mmol scale) after 3 h at room temperature as a clear, colorless oil: ^{1}H NMR (400 MHz) δ 7.36-7.20 (m, 5 H), 6.64 (br d, *J* = 16.0 Hz, 1 H), 6.26 (dt, *J* = 16.0, 6.0 Hz, 1 H), 4.75 (d, *J* = 6.4 Hz, 2 H), 3.76 (s, 3 H); ^{13}C NMR (100 MHz) δ 155.2, 135.7, 134.3, 128.3, 127.8, 126.3, 122.1, 68.2, 54.6; IR ($CDCl_3$) 3051, 2984, 2304, 1746, 1442, 1421, 1272 cm^{-1}; mass spectrum (CI) *m*/*z* 192.0778 [$C_{11}H_{12}O_3$ (M+1) requires 192.0786] 192, 145, 117 (base).

NMR Assignments: ^{1}H NMR (400 MHz) δ 7.36-7.20 (m, 5 H, C5-C6-C7-H), 6.64 (br d, *J* = 16.0 Hz, 1 H, C3-H), 6.26 (dt, *J* = 16.0, 6.0 Hz, 1 H, C2-H), 4.75 (d, *J* = 6.4 Hz, 2 H, C1-H), 3.76 (s, 3 H, C9-H); ^{13}C NMR (100 MHz) δ 155.2 (C8), 135.7 (C4), 134.3 (C3), 128.3 (C6), 127.8 (C7), 126.3 (C5), 122.1 (C2), 68.2 (C9), 54.6 (C1).

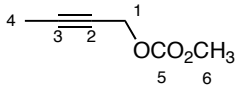


3.14j

Carbonic acid methyl ester 3-methyl-2-butenyl ester (3.14j) (BLA-II-176). Carbonate **3.14j** was obtained in 95% yield (5.8 mmol scale) after 1.5 h at room temperature as a clear, colorless oil: ^{1}H NMR (300 MHz) δ 5.38 (dddt, *J* = 8.7, 6.0, 2.7, 1.2 Hz, 1 H), 4.63 (d, *J* = 7.5 Hz, 2 H), 3.78 (s, 3 H), 1.76 (s, 3 H), 1.73 (s, 3 H); ^{13}C

NMR (62.5 MHz) δ 155.6, 139.5, 117.9, 64.3, 54.2, 25.4, 17.6; mass spectrum (CI) *m/z* 144.0780 [$C_7H_{12}O_3$ (M) requires 144.0786] 145, 137, 69 (base).

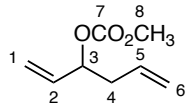
NMR Assignments: ^{1}H NMR (300 MHz) δ 5.38 (dddt, *J* = 8.7, 6.0, 2.7, 1.2 Hz, 1 H, C2-H), 4.63 (d, *J* = 7.5 Hz, 2 H, C1-H), 3.78 (s, 3 H, C7-H), 1.76 (s, 3 H, C4-H), 1.73 (s, 3 H, C5-H); ^{13}C NMR (62.5 MHz) δ 155.6 (C6), 139.5 (C3), 117.9 (C2), 64.3 (C7), 54.2 (C1), 25.4 (C4), 17.6 (C5).



3.14k

Carbonic acid but-2-ynyl ester methyl ester (3.14k) (BLA-IV-146). Carbonate **3.14k** was obtained in 88% yield (14.3 mmol scale) after 6 h at room temperature as a clear, red oil: ^{1}H NMR (400 MHz) δ 4.69 (q, *J* = 2.4 Hz, 2 H), 3.79 (s, 3 H), 1.85 (t, *J* = 2.4 Hz, 3 H); ^{13}C NMR (100 MHz) δ 154.9, 83.5, 72.3, 55.7, 54.5, 3.1; IR ($CDCl_3$) 2957, 2258, 1746, 1446, 1375, 1281, 1156, 947 cm^{-1}; mass spectrum (CI) *m/z* 129.0553 [$C_6H_9O_3$ (M+1) requires 129.0552] 129, 113, 105 (base).

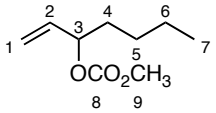
NMR Assignments: ^{1}H NMR (400 MHz) δ 4.69 (q, *J* = 2.4 Hz, 2 H, C1-H), 3.79 (s, 3 H, C6-H), 1.85 (t, *J* = 2.4 Hz, 3 H, C4-H); ^{13}C NMR (100 MHz) δ 154.9 (C5), 83.5 (C2), 72.3 (C3), 55.7 (C4), 54.5 (C6), 3.1 (C1).



3.14m

Carbonic acid methyl ester 1-vinyl-3-butenyl ester (3.14m) (BLA-III-298). Carbonate **3.14m** was obtained in 100% yield (5.1 mmol scale) after 3 h at room temperature as a clear, colorless oil: ^{1}H NMR (400 MHz) □ 5.81 (ddd, *J* = 17.6, 10.4, 6.8 Hz, 1 H), 5.75 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.31 (dt, *J* = 17.2, 1.2 Hz, 1 H), 5.22 (dt, *J* = 10.8, 1.2 Hz, 1 H), 5.15-5.09 (comp, 3H), 3.77 (s, 3 H), 2.44 (dddt, *J* = 13.6, 7.6, 7.2, 6.8 Hz, 2 H); ^{13}C NMR (100 MHz) □ 154.9, 135.1, 132.5, 118.1, 117.5, 77.9, 54.6, 38.8; IR ($CDCl_3$) 3083, 2984, 2957, 2258, 1740, 1443, 1338, 1271, 1045 cm^{-1}; mass spectrum (CI) *m/z* 157.0859 [$C_8H_{13}O_3$ (M+1) requires 157.0865] 157, 115, 81 (base).

NMR Assignments: ^{1}H NMR (400 MHz) □ 5.81 (ddd, *J* = 17.6, 10.4, 6.8 Hz, 1 H, C2-H), 5.75 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1 H, C5-H), 5.31 (dt, *J* = 17.2, 1.2 Hz, 1 H, C1-H), 5.22 (dt, *J* = 10.8, 1.2 Hz, 1 H, C1-H), 5.15-5.09 (comp, 3H, C6-C3-H), 3.77 (s, 3 H, C8-H), 2.44 (dddt, *J* = 13.6, 7.6, 7.2, 6.8 Hz, 2 H, C4-H); ^{13}C NMR (100 MHz) □ 154.9 (C7), 135.1 (C2), 132.5 (C5), 118.1 (C1), 117.5 (C6), 77.9 (C3), 54.6 (C8), 38.8 (C4).

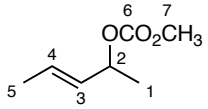


3.14n

Carbonic acid 1-butylallyl ester methyl ester (3.14n) (BLA-IV-59). Carbonate **3.14n** was obtained in 69% yield (4.38 mmol scale) after 3 h at room temperature as a

clear, colorless oil after chromatography (pentane/Et_2O = 5:1): ^{1}H NMR (400 MHz) δ 5.79 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.28 (app dt, *J* = 17.6, 0.8 Hz, 1 H), 5.19 (app dt, *J* = 10.4, 1.2 Hz, 1 H), 5.04 (app dt, *J* = 13.2, 6.8 Hz, 1 H), 3.76 (s, 3 H), 1.75-1.66 (m, 1 H), 1.65-1.56 (m, 1 H), 1.38-1.29 (m, 4 H), 0.90 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz) δ 154.9, 135.8, 116.9, 78.3, 54.3, 33.8, 27.0, 22.3, 13.8; IR ($CDCl_3$) 2958, 2862, 2260, 1743, 1443, 1270 cm^{-1}; mass spectrum (CI) *m/z* 173.1177 [$C_7H_{13}O_3$ (M+1) requires 173.1178] 173, 97 (base).

NMR Assignments: ^{1}H NMR (400 MHz) δ 5.79 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H, C2-H), 5.28 (app dt, *J* = 17.6, 0.8 Hz, 1 H, C1-H), 5.19 (app dt, *J* = 10.4, 1.2 Hz, 1 H, C1-H), 5.04 (app dt, *J* = 13.2, 6.8 Hz, 1 H, C3-H), 3.76 (s, 3 H, C9-H), 1.75-1.66 (m, 1 H, C4-H), 1.65-1.56 (m, 1 H, C4-H), 1.38-1.29 (m, 4 H, C5-C6-H), 0.90 (t, *J* = 7.2 Hz, 3 H, C7-H); ^{13}C NMR (100 MHz) δ 154.9 (C8), 135.8 (C2), 116.9 (C1), 78.3 (C3), 54.3 (C9), 33.8 (C4), 27.0 (C5), 22.3 (C6), 13.8 (C7).

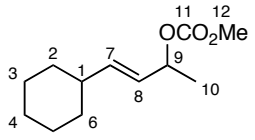


3.14p

***trans*-Carbonic acid methyl ester 1-methylbut-2-enyl ester (3.14p) (BLA-IV-286)**. Carbonate **3.14p** was obtained in 98% yield (34.6 mmol scale) after 3 h at room temperature as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1): ^{1}H NMR (400 MHz) δ 5.77 (ddd, *J* = 15.4, 6.8, 1.0 Hz, 1 H), 5.49 (ddq, *J* = 15.4, 7.2, 1.4 Hz, 1 H), 5.14 (app pent, *J* = 6.5 Hz, 1 H), 3.76 (s, 3 H), 1.70 (dd, *J* = 6.2, 1.4 Hz, 3 H), 1.34 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz) δ 154.8, 129.9, 128.7, 75.2, 54.2, 20.3, 17.6; IR

($CHCl_3$) 3034, 2986, 1741, 1443, 1276 cm^{-1}; mass spectrum (CI) *m/z* 145.0862 [$C_7H_{13}O_3$ (M+1) requires 145.0865] 145, 137 (base).

NMR Assignments: ^{1}H NMR (400 MHz) δ 5.77 (ddd, *J* = 15.4, 6.8, 1.0 Hz, 1 H, C4-H), 5.49 (ddq, *J* = 15.4, 7.2, 1.4 Hz, 1 H, C3-H), 5.14 (app pent, *J* = 6.5 Hz, 1 H, C2-H), 3.76 (s, 3 H, C7-H), 1.70 (dd, *J* = 6.8, 1.4 Hz, 3 H, C5-H), 1.34 (d, *J* = 6.5 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz) δ 154.8 (C6), 129.9 (C3), 128.7 (C4), 75.2 (C2), 54.2 (C7), 20.3 (C1), 17.6 (C5).

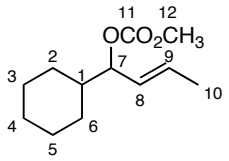


3.14r

Carbonic acid 3-cyclohexyl-1-methylallyl ester methyl ester (3.14r). (BLA-VI-100). Carbonate **3.14r** was obtained in 86% yield (0.58 mmol scale) after 30 min at room temperature as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1): ^{1}H NMR (400 MHz) δ 5.69 (dd, *J* = 15.6, 6.4 Hz, 1 H), 5.42 (ddd, *J* = 15.6, 7.2, 1.2 Hz, 1 H), 5.15 (dq, *J* = 6.8, 6.4 Hz, 1 H), 3.76 (s, 3 H), 1.98-1.91 (m, 1 H), 1.73-1.62 (comp, 5 H), 1.34 (d, *J* = 6.8 Hz, 3 H), 1.31-1.01 (comp, 5 H); ^{13}C NMR (100 MHz) δ 155.0, 139.7, 126.2, 75.6, 54.3, 40.1, 32.4, 32.4, 26.0, 25.9, 20.3; IR ($CHCl_3$) 3018, 2928, 2853, 1742, 1444, 1275 cm^{-1}; mass spectrum (CI) *m/z* 212.1412 [$C_{12}H_{20}O_3$ (M) requires 212.1402] 213, 137 (base).

NMR Assignments: ^{1}H NMR (400 MHz) δ 5.69 (dd, *J* = 15.6, 6.4 Hz, 1 H, C8-H), 5.42 (ddd, *J* = 15.6, 7.2, 1.2 Hz, 1 H, C7-H), 5.15 (dq, *J* = 6.8, 6.4 Hz, 1 H, C9-H), 3.76 (s, 3 H, C12-H), 1.98-1.91 (m, 1 H, C1-H), 1.73-1.62 (comp, 5 H), 1.34 (d, *J* = 6.8

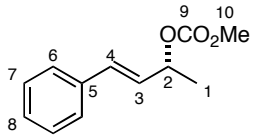
Hz, 3 H, C10-H), 1.31-1.01 (comp, 5 H); ^{13}C NMR (100 MHz) 155.0 (C11), 139.7 (C7), 126.2 (C8), 75.6 (C9), 54.3 (C12), 40.1, 32.4, 32.4, 26.0, 25.9, 20.3 (C10).



3.14s

(*E*)-1-cyclohexylbut-2-enyl methyl carbonate (3.14s) (BLA-IV-262). Carbonate **3.14s** was obtained in 97% yield (0.65 mmol scale) after 6 h at room temperature as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1): ^{1}H NMR (400 MHz) 5.75 (dq, *J* = 14.8, 6.4 Hz, 1 H), 5.41 (ddq, *J* = 14.8, 6.4, 1.6 Hz, 1 H), 4.78 (app t, *J* = 7.6 Hz, 1 H), 3.76 (s, 3 H), 1.81-1.63 (m, 5 H), 1.71 (dd, *J* = 6.4, 1.6 Hz, 3 H), 1.59-1.50 (m, 1 H), 1.27-1.11 (m, 3 H), 1.03-0.91 (m, 2 H); ^{13}C NMR (100 MHz) 155.3, 130.7, 127.6, 83.5, 54.3, 41.5, 28.5, 28.4, 26.2, 25.8, 25.7, 17.7; IR ($CHCl_3$) 2931, 2360, 1741, 1442, 1275, 969 cm^{-1}; mass spectrum (CI) *m/z* 213.1482 [$C_{12}H_{21}O_3$ (M+1) requires 213.1491] 273 (base), 213.

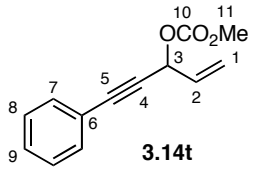
NMR Assignments: ^{1}H NMR (400 MHz) 5.75 (dq, *J* = 14.8, 6.4 Hz, 1 H, C9-H), 5.41 (ddq, *J* = 14.8, 6.4, 1.6 Hz, 1 H, C8-H), 4.78 (app t, *J* = 7.6 Hz, 1 H, C7-H), 3.76 (s, 3 H, C12-H), 1.81-1.63 (m, 5 H), 1.71 (dd, *J* = 6.4, 1.6 Hz, 3 H, C10-H), 1.59-1.50 (m, 1 H, C1-H), 1.27-1.11 (m, 3 H), 1.03-0.91 (m, 2 H); ^{13}C NMR (100 MHz) 155.3 (C11), 130.7 (C13), 127.6 (C2), 83.5 (C4), 54.3 (C12), 41.5 (C5), 28.5 (C_{Hex}), 28.4 (C_{Hex}), 26.2 (C_{Hex}), 25.8 (C_{Hex}), 25.7 (C_{Hex}), 17.7 (C1).



(+)-3.47

Carbonic acid methyl ester 1-methyl-3-phenylallyl ester ((+)-3.47) (BLA-VI-79). Carbonate **(+)-3.47** was obtained in 87% yield (1.34 mmol scale) after 30 min at room temperature as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1): ^1H NMR (400 MHz) 7.39-7.36 (m, 2 H), 7.32-7.27 (m, 2 H), 7.26-7.21 (m, 1 H), 6.64 (d, *J* = 16.0 Hz, 1 H), 6.19 (dd, *J* = 16.0, 7.2 Hz, 1 H), 5.37 (ddq, *J* = 7.2, 6.4, 1.2 Hz, 1 H), 3.76 (s, 3 H), 1.46 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz) 155.0, 136.0, 132.1, 128.4, 127.9, 127.8, 126.5, 75.1, 54.4, 20.3; IR ($CHCl_3$) 3025, 2958, 1743, 1443, 1274, 1036, 967, 942 cm^{-1}; mass spectrum (CI) *m/z* 206.0945 [$C_{12}H_{14}O_3$ (M) requires 206.0943] 207, 131 (base).

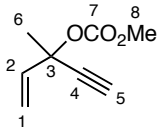
NMR Assignments: ^1H NMR (400 MHz) 7.39-7.36 (m, 2 H, C_{AR}-H), 7.32-7.27 (m, 2 H, C_{AR}-H), 7.26-7.21 (m, 1 H, C4-H), 6.64 (d, *J* = 16.0 Hz, 1 H, C4-H), 6.19 (dd, *J* = 16.0, 7.2 Hz, 1 H, C3-H), 5.37 (ddq, *J* = 7.2, 6.4, 1.2 Hz, 1 H, C2-H), 3.76 (s, 3 H, C10-H), 1.46 (d, *J* = 6.5 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz) 155.0 (C9), 136.0 (C5), 132.1, 128.4, 127.9, 127.8, 126.5, 75.1 (C2), 54.4 (C10), 20.3 (C1).



3.14t

Carbonic acid methyl ester 1-phenylethynyl-allyl ester (3.14t) (BLA-VI-68). *n*-BuLi (9.1 mL, 2.34 M in hexanes) was added to a solution of phenylacetylene (2.19 g, 2.35 mL, 21.4 mmol) in THF (36 mL) at –78 ˚C, and the resultant solution was stirred for 1 h. Acrolein (**3.17**) (1.00 g, 0.84 mL, 17.8 mmol) was added at –78 ˚C, and stirred for 1 h. Methyl chloroformate (2.53 g, 2.1 mL, 26.7 mmol) was then added, the cooling bath was removed, and the resulting mixture was stirred at room temperature for 2 h. Et_2O (10 mL) was added and the solution was washed sequentially with H_2O (2 x 20 mL) and saturated aqueous NaCl (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. A 250 mg aliquot of the crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to provide **3.14t** as a clear colorless oil: ^{1}H NMR (400 MHz) □ 7.59-7.57 (m, 1 H), 7.48-7.42 (m, 2 H), 7.39-7.28 (m, 2 H), 6.06-5.96 (comp, 2 H), 5.65 (dd, *J* = 16.4, 1.6 Hz, 1 H), 5.39 (dd, *J* = 9.6, 1.6 Hz, 1 H), 3.82 (s, 3 H); ^{13}C NMR (100 MHz) □ 154.7, 132.9, 131.8, 128.8, 128.5, 128.2, 119.5, 87.6, 83.5, 68.7, 54.9; IR ($CHCl_3$) 3022, 2957, 2227, 1749, 1443, 1286, 941 cm^{-1}; mass spectrum (CI) *m/z* 216.0781 [$C_{13}H_{12}O_3$ (M) requires 216.0786] 217, 173, 161, 141 (base).

NMR Assignments: ^{1}H NMR (400 MHz) □ 7.59-7.57 (m, 1 H, C4-H, C_{AR}-H), 7.48-7.42 (m, 2 H, C_{AR}-H), 7.39-7.28 (m, 2 H, C_{AR}-H), 6.06-5.96 (comp, 2 H, C9-C10-H), 5.65 (dd, *J* = 16.4, 1.6 Hz, 1 H, C11-H), 5.39 (dd, *J* = 9.6, 1.6 Hz, 1 H, C11-H), 3.82 (s, 3 H, C13-H); ^{13}C NMR (100 MHz) □ 154.7 (C12), 132.9 (C10), 131.8, 128.8, 128.5, 128.2, 119.5 (C11), 87.6 (C8), 83.5 (C7), 68.7 (C9), 54.9 (C13).

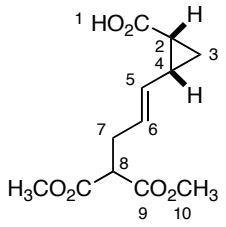


3.14u

Carbonic acid 1-ethynyl-1-methyl-allyl ester methyl ester (3.14u) (BLA-VI-66). Ethynyl magnesium bromide (34 mL, 0.5 M in THF) was added to a solution of methyl vinyl ketone (1.00 g, 0.84 mL, 14.3 mmol) in THF (30 mL) at –78 ˚C and stirred for 20 min. Methyl chloroformate (2.02 g, 1.65 mL, 21.4 mmol) was added to the dark brown solution at –78 ˚C, the cooling bath was removed, and the mixture was stirred at room temperature for 4 h. Et_2O (10 mL) was added, and the solution washed sequentially with H_2O (2 x 20 mL) and saturated aqueous NaCl (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. A 250 mg aliquot of the crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to provide **3.14u** as a clear colorless oil: ^{1}H NMR (400 MHz) 5.99 (dd, J = 17.1, 10.3 Hz, 1 H), 5.65 (d, J = 17.1 Hz, 1 H), 5.30 (d, J = 10.3 Hz, 1 H), 3.77 (s, 3 H), 2.73 (s, 1 H), 1.74 (s, 3 H); ^{13}C NMR (100 MHz) 153.3, 137.5, 116.8, 81.3, 76.1, 75.5, 54.4, 28.4; IR ($CHCl_3$) 3306, 3027, 2958, 1755, 1442, 1275, 1059, 941, 886 cm^{-1}; mass spectrum (CI) m/z 155.0703 [$C_8H_{11}O_3$ (M+1) requires 155.0708] 187 (base), 155, 141, 111.

NMR Assignments: ^{1}H NMR (400 MHz) 5.99 (dd, J = 17.1, 10.3 Hz, 1 H, C2-H), 5.65 (d, J = 17.1 Hz, 1 H, C1-H), 5.30 (d, J = 10.3 Hz, 1 H, C1-H), 3.77 (s, 3 H, C8-H), 2.73 (s, 1 H, C5-H), 1.74 (s, 3 H, C6-H); ^{13}C NMR (100 MHz) 153.3 (C7), 137.5 (C2), 116.8 (C1), 81.3 (C4), 76.1, 75.5, 54.4 (C8), 28.4 (C6).

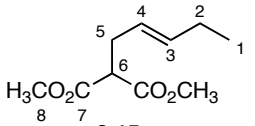
General procedure for the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation of unsymmetrical allylic carbonates with dimethyl malonate. $[Rh(CO)_2Cl]_2$ (19.0 mg, 5 mol %) was dissolved in the indicated degassed solvent (5 mL) and stirred for 5-10 min at room temperature. The allylic carbonate **3.14** (1.0 mmol) was added and the solution stirred for 30 min. In a separate flask, dimethyl malonate (330 mg, 0.29 mL, 2.5 mmol) was added to a slurry of NaH (40 mg of a 60% mineral oil suspension, 2.0 mmol) in the indicated degassed solvent (5 mL) and stirred for 20 min at room temperature. The resulting malonate anion was added *via* syringe to the solution of allylic substrate and $[Rh(CO)_2Cl]_2$ at room temperature. The mixture was then stirred for the indicated time at the indicated temperature. **General Workup A:** Saturated aqueous $NaHCO_3$ (10 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. **General Workup B:** The reaction was filtered through a short plug of silica gel eluting with Et_2O (50 mL), and the combined filtrate was concentrated under reduced pressure. **General Workup C:** Saturated aqueous NH_4Cl (10 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL), and the combined organic fractions were washed with saturated aqueous NaCl (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O to provide the alkylation products **3.15/3.16** in the specified ratio.



3.10

2-[3-[2*R*,3*R*]-(2-Carboxycyclopropyl)-allyl]-malonic acid dimethyl ester (3.10). (BLA-IV-61). Malonate **3.10** was obtained in 93% yield (0.40 mmol scale) after 1 h in THF at room temperature. Aqueous 1 M $NaHSO_4$ (2.5 mL) was added to the reaction and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 3 mL) and the combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to give 96 mg (93%) of **3.10** as a clear, pale yellow oil: ^{1}H NMR (400 MHz) 5.64 (app dt, *J* = 15.2, 6.8 Hz, 1 H), 5.53 (dd, *J* = 15.6, 8.8 Hz, 1 H), 3.72 (s, 3 H), 3.71 (s, 3 H), 3.42 (t, *J* = 7.2 Hz, 1 H), 2.61 (app t, *J* = 7.2 Hz, 2 H), 1.96 (app dt, *J* = 8.8, 8.4 Hz, 1 H), 1.88 (ddd, *J* = 14.0, 8.0, 6.0 Hz, 1 H), 1.29-1.21 (m, 2 H); ^{13}C NMR (100 MHz) 177.9, 169.0, 129.7, 127.6, 52.5, 52.4, 51.8, 31.8, 24.7, 20.7, 15.0; IR ($CDCl_3$) 3010, 2955, 2258, 1733, 1698, 1437, 1234, 1161 cm^{-1}; mass spectrum (CI) *m/z* 257.1031 [$C_{12}H_{17}O_6$ (M+1) requires 257.1025] 257, 239 (base), 207, 179.

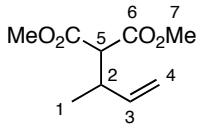
NMR Assignments: ^{1}H NMR (400 MHz) 5.64 (app dt, *J* = 15.2, 6.8 Hz, 1 H, C6-H), 5.53 (dd, *J* = 15.6, 8.8 Hz, 1 H, C5-H), 3.72 (s, 3 H, C11-H), 3.71 (s, 3 H, C12-H), 3.42 (t, *J* = 7.2 Hz, 1 H, C8-H), 2.61 (app t, *J* = 7.2 Hz, 2 H, C7-H), 1.96 (app dt, *J* = 8.8, 8.4 Hz, 1 H, C2-H), 1.88 (ddd, *J* = 14.0, 8.0, 6.0 Hz, 1 H, C4-H), 1.29-1.21 (m, 2 H, C3-H); ^{13}C NMR (100 MHz) 177.9 (C1), 169.0 (C9), 129.7 (C5), 127.6 (C6), 52.5 (C11), 52.4 (C12), 51.8 (C8), 31.8 (C7), 24.7 (C2), 20.7 (C4), 15.0 (C3).



3.15a

***trans*-2-Pent-2-enylmalonic acid dimethyl ester (3.15a). (BLA-IV-120).** Malonate **3.15a** was obtained in 84% yield (0.34 mmol scale) after 2 h in THF at room temperature (General Workup A) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 98:2 regioisomeric ratio: ^{1}H NMR (400 MHz) 5.56 (dddt, *J* = 15.2, 6.8, 5.2, 1.6 Hz, 1 H), 5.34 (dddt, *J* = 15.2, 7.2, 5.2, 1.6 Hz, 1 H), 3.73 (s, 3 H), 3.41 (t, *J* = 7.6 Hz, 1 H), 2.58 (app dt, *J* = 8.0, 1.2 Hz, 2 H), 2.02-1.95 (m, 2 H), 0.94 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz) 169.2, 135.5, 123.9, 52.4, 52.0, 31.9, 25.6, 13.8; IR ($CDCl_3$) 2955, 1731, 1436, 1272, 1232, 1158 cm^{-1}; mass spectrum (CI) *m/z* 201.1117 [$C_{10}H_{17}O_4$ (M+1) requires 201.1127] 201 (base), 169.

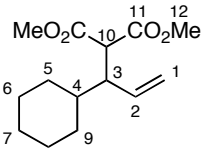
NMR Assignments: ^{1}H NMR (400 MHz) 5.56 (dddt, *J* = 15.2, 6.8, 5.2, 1.6 Hz, 1 H, C4-H), 5.34 (dddt, *J* = 15.2, 7.2, 5.2, 1.6 Hz, 1 H, C3-H), 3.73 (s, 3 H, C8-H), 3.41 (t, *J* = 7.6 Hz, 1 H, C6-H), 2.58 (app dt, *J* = 8.0, 1.2 Hz, 2 H, C5-H), 2.02-1.95 (m, 2 H, C2-H), 0.94 (t, *J* = 7.2 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz) 169.2 (C1), 135.5 (C4), 123.9 (C5), 52.4 (C8), 52.0 (C2), 31.9 (C3), 25.6 (C6), 13.8 (C7).



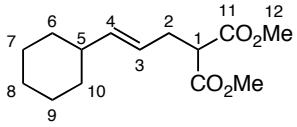
3.15b

2-(1-Methylallyl)-malonic acid dimethyl ester (3.15b) (BLA-V-203). Malonate **3.15b** was obtained in 93% yield (0.38 mmol scale) after 3 h in DMF at –20 ˚C (General

Workup C) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 80:20 regioisomeric ratio: ^{1}H NMR is consistent with the assigned structure.[385]



3.15d

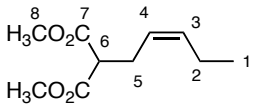


3.16d

2-(1-Cyclohexylallyl)-malonic acid dimethyl ester (3.15d) (BLA-VI-64). Malonate **3.15d** was obtained in 97% yield (0.25 mmol scale) after 24 h in THF at rt (General Workup B) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 79:21 regioisomeric ratio: **Regioisomer 3.16d:** ^{1}H NMR (400 MHz) □ 5.43 (dt, *J* = 15.6, 6.8 Hz, 1 H), 5.34-5.27 (m, 1 H), 3.73 (s, 6 H), 3.40 (t, *J* = 7.2 Hz, 1 H), 2.57 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 2 H), 1.92-1.85 (m, 1 H), 1.71-1.62 (m, 4 H), 1.29-0.96 (m, 6 H); ^{13}C NMR (100 MHz) □ 169.4, 137.6, 122.6, 52.4, 52.0, 31.8, 13.4, 6.5; **Regioisomer 3.15d:** ^{1}H NMR (400 MHz) □ 5.82 (ddd, *J* = 18.0, 10.0, 7.6 Hz, 1 H), 5.10-5.04 (comp, 2 H), 3.74 (s, 6 H), 3.54 (d, *J* = 8.8 Hz, 1 H), 2.12 (ddd, *J* = 17.6, 8.8, 8.8 Hz, 1 H), 0.87-0.84 (m, 1 H), 0.49 (ddd, *J* = 8.0, 2.8, 1.6 Hz, 2 H), 0.25-0.22 (m, 1 H), 0.15-0.11 (m, 1 H); IR ($CHCl_3$) 2927, 2853, 2362, 1732, 1437, 1265, 1159 cm^{-1}; mass spectrum (CI) *m/z* 213.1118 [$C_{11}H_{17}O_4$ (M+1) requires 213.1127] 213 (base).

NMR Assignments: Regioisomer 3.16d: ^{1}H NMR (400 MHz) □ 5.43 (dt, *J* = 15.6, 6.8 Hz, 1 H, C4-H), 5.34-5.27 (m, 1 H, C3-H), 3.73 (s, 6 H, C12-H), 3.40 (t, *J* = 7.2 Hz, 1 H, C1-H), 2.57 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 2 H, C2-H), 1.92-1.85 (m, 1 H, C5-H), 1.71-1.62 (m, 4 H, C_{HEX}-H), 1.29-0.96 (m, 6 H, C_{HEX}-H); ^{13}C NMR (100 MHz) □ 169.4 (C11), 140.1 (C4), 122.6 (C3), 52.4 (C12), 52.0 (C1), 40.5 (C5), 31.8 (C2), 31.9, 26.3,

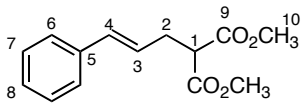
26.0, 25.9; **Regioisomer 3.15d:** ^{1}H NMR (400 MHz) □ 5.82 (ddd, *J* = 18.0, 10.0, 7.6 Hz, 1 H, C2-H), 5.10-5.04 (comp, 2 H, C1-H), 3.74 (s, 6 H, C12-H), 3.54 (d, *J* = 8.8 Hz, 1 H, C10-H), 2.12 (ddd, *J* = 17.6, 8.8, 8.8 Hz, 1 H, C3-H).



3.15e

***cis*-2-Pent-2-enylmalonic acid dimethyl ester (3.15e)**. **(BLA-IV-121)**. Malonate **3.15e** was obtained in 86% yield (0.34 mmol scale) after 12 h in THF at 0 ˚C (General Workup A) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 99:1 regioisomeric ratio and 97:3 cis/trans ratio: ^{1}H NMR (400 MHz) □ 5.58 (dddt, *J* = 10.4, 8.8, 7.2, 1.2 Hz, 1 H), 5.25 (dddt, *J* = 10.8, 9.2, 7.6, 2.0 Hz, 1 H), 3.73 (s, 6 H), 3.39 (t, *J* = 7.2 Hz, 1 H), 2.67-2.63 (m, 2 H), 2.11-2.03 (m, 2 H), 0.96 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz) □ 169.2, 134.8, 123.6, 52.5, 51.8, 26.7, 20.6, 14.2; IR ($CDCl_3$) 2956, 2258, 1732, 1437, 1240, 1158 cm^{-1}; mass spectrum (CI) *m/z* 201.1124 [$C_{10}H_{17}O_4$ (M+1) requires 201.1127] 201 (base), 169.

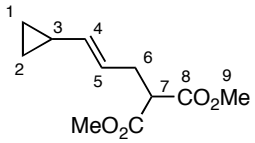
NMR Assignments: ^{1}H NMR (400 MHz) □ 5.58 (dddt, *J* = 10.4, 8.8, 7.2, 1.2 Hz, 1 H, C4-H), 5.25 (dddt, *J* = 10.8, 9.2, 7.6, 2.0 Hz, 1 H, C3-H), 3.73 (s, 6 H, C8-H), 3.39 (t, *J* = 7.2 Hz, 1 H, C6-H), 2.67-2.63 (m, 2 H, C5-H), 2.11-2.03 (m, 2 H, C2-H), 0.96 (t, *J* = 7.6 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz) □ 169.2 (C7), 134.8 (C4), 123.6 (C3), 52.5 (C8), 51.8 (C6), 26.7 (C5), 20.6 (C2), 14.2 (C1).



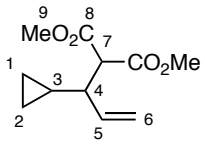
3.15f

2-(3-Phenylallyl)-malonic acid dimethyl ester (3.15f). (BLA-IV-212). Malonate **3.15f** was obtained in 93% yield (0.26 mmol scale) after 2 h in THF at 0 ˚C (General Workup A) as a clear, pale yellow oil after chromatography (pentane/Et_2O = 5:1) in a 90:10 regioisomeric ratio: ^{1}H NMR (400 MHz) □ 7.35-7.19 (comp, 5 H), 6.48 (d, *J* = 15.6 Hz, 1 H), 6.14 (dt, *J* = 15.6, 7.2 Hz, 1 H), 3.75 (s, 6 H), 3.53 (t, *J* = 7.2 Hz, 1 H), 2.81 (ddd, *J* = 9.2, 7.6, 2.0 Hz, 2 H); ^{13}C NMR (100 MHz) □ 169.2, 132.9, 128.4, 127.4, 126.1, 52.5, 51.7, 32.3; IR ($CDCl_3$) 3029, 2954, 2259, 1732, 1437, 1265, 1234, 1201, 1157 cm^{-1}; mass spectrum (CI) *m/z* 249.1127 [$C_{14}H_{17}O_4$ (M+1) requires 249.1127] 249 (base).

NMR Assignments: ^{1}H NMR (400 MHz) □ 7.35-7.19 (comp, 5 H, C6-C7-C8-H), 6.48 (d, *J* = 15.6 Hz, 1 H, C4-H), 6.14 (dt, *J* = 15.6, 7.2 Hz, 1 H, C3-H), 3.75 (s, 6 H, C10-H), 3.53 (t, *J* = 7.2 Hz, 1 H, C1-H), 2.81 (ddd, *J* = 9.2, 7.6, 2.0 Hz, 2 H, C2-H); ^{13}C NMR (100 MHz) □ 169.2 (C9), 132.9 (C5), 128.4, 127.4, 126.1, 52.5 (C10), 51.7 (C1), 32.3 (C2).



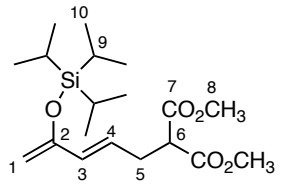
3.15g



3.16g

2-(3-Cyclopropylallyl)-malonic acid dimethyl ester (3.15g) (BLA-V-131). Malonate **3.15g** was obtained in 84% yield (0.32 mmol scale) after 20 h in THF at 0 ˚C (General Workup A) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 89:11 regioisomeric ratio: **Regioisomer 3.15g:** ^{1}H NMR (400 MHz) □ 5.43 (dt, *J* = 15.6, 6.8 Hz, 1 H), 5.13-5.04 (comp, 1 H), 3.73 (s, 6 H), 3.40 (t, *J* = 7.2 Hz, 1 H), 2.57 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 2 H), 1.37-1.28 (m, 1 H), 0.68-0.64 (m, 2 H), 0.33-0.29 (m, 2 H); ^{13}C NMR (100 MHz) □ 169.4, 137.6, 122.6, 52.4, 52.0, 31.8, 13.4, 6.5; **Regioisomer 3.16g:** ^{1}H NMR (400 MHz) □ 5.82 (ddd, *J* = 18.0, 10.0, 7.6 Hz, 1 H), 5.10-5.04 (comp, 2 H), 3.74 (s, 6 H), 3.54 (d, *J* = 8.8 Hz, 1 H), 2.12 (dt, *J* = 17.6, 8.8 Hz, 1 H), 0.87-0.84 (m, 1 H), 0.49 (ddd, *J* = 8.0, 2.8, 1.6 Hz, 2 H), 0.25-0.22 (m, 1 H), 0.15-0.11 (m, 1 H); IR ($CHCl_3$) 3033, 2955, 1733, 1437, 1265, 1232, 1156, 909 cm^{-1}; mass spectrum (CI) *m*/*z* 213.1118 [$C_{11}H_{17}O_4$ (M+1) requires 213.1127] 213 (base).

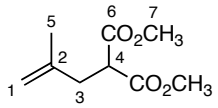
NMR Assignments: Regioisomer 3.15g: ^{1}H NMR (400 MHz) □ 5.43 (dt, *J* = 15.6, 6.8 Hz, 1 H, C5-H), 5.13-5.04 (comp, 1 H, C4-H), 3.73 (s, 6 H, C9-H), 3.40 (t, *J* = 7.2 Hz, 1 H, C7-H), 2.57 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 2 H, C6-H), 1.37-1.28 (m, 1 H, C3-H), 0.68-0.64 (m, 2 H, C1-H), 0.33-0.29 (m, 2 H, C2-H); ^{13}C NMR (100 MHz) □ 169.4 (C8), 137.6 (C4), 122.6 (C5), 52.4 (C9), 52.0 (C7), 31.8 (C6), 13.4 (C3), 6.5 (C1,2); **Regioisomer 3.16g:** ^{1}H NMR (400 MHz) □ 5.82 (ddd, *J* = 18.0, 10.0, 7.6 Hz, 1 H, C5-H), 5.10-5.04 (comp, 2 H, C6-H), 3.74 (s, 6 H, C9-H), 3.54 (d, *J* = 8.8 Hz, 1 H, C7-H), 2.12 (dt, *J* = 17.6, 8.8 Hz, 1 H, C4-H), 0.87-0.84 (m, 1 H, C3-H), 0.49 (ddd, *J* = 8.0, 2.8, 1.6 Hz, 2 H, C1-H), 0.25-0.22 (m, 1 H, C2-H), 0.15-0.11 (m, 1 H, C2-H).



3.15h

2-[4-(Triisopropylsilanyloxy)-penta-2,4-dienyl]malonic acid dimethyl ester (3.15h). **(BLA-VI-132)**. Malonate **3.15h** was obtained in 94% yield (0.32 mmol scale) after 12 h in DMF at room temperature (General Workup B) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 97:3 regioisomeric ratio: ^{1}H NMR (400 MHz) 5.97-5.95 (comp, 2 H), 4.26 (s, 1 H), 4.21 (s, 1 H), 3.73 (s, 6 H), 3.46 (t, *J* = 7.6 Hz, 1 H), 2.70 (ddd, *J* = 7.6, 6.0, 3.2 Hz, 2 H), 1.21 (app q, *J* = 6.8 Hz, 3 H), 1.08 (d, *J* = 6.8 Hz, 18 H); ^{13}C NMR (100 MHz) 169.2, 154.6, 130.9, 125.9, 94.4, 52.5, 51.6, 31.4, 18.0, 12.7; IR ($CHCl_3$) 2948, 2868, 1734, 1592, 1437, 1320, 1286, 1158, 1026 cm^{-1}; mass spectrum (CI) *m/z* 371.1904 [$C_{18}H_{31}O_6Si$ (M+1) requires 371.1890] 371, 215, 176, 159, 135 (base).

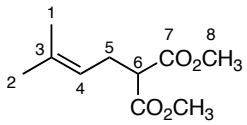
NMR Assignments: ^{1}H NMR (400 MHz) 5.97-5.95 (comp, 2 H, C3-C4-H), 4.26 (s, 1 H, C1-H), 4.21 (s, 1 H, C1-H), 3.73 (s, 6 H, C8-H), 3.46 (t, *J* = 7.6 Hz, 1 H, C6-H), 2.70 (ddd, *J* = 7.6, 6.0, 3.2 Hz, 2 H, C5-H), 1.21 (app q, *J* = 6.8 Hz, 3 H, C9-H), 1.08 (d, *J* = 6.8 Hz, 18 H, C10-H); ^{13}C NMR (100 MHz) 169.2 (C7), 154.6 (C2), 130.9 (C4), 125.9 (C3), 94.4 (C1), 52.5 (C6), 51.6 (C8), 31.4 (C5), 18.0 (C10), 12.7 (C9).



3.15i

2-(2-Methylallyl)-malonic acid dimethyl ester (3.15i). **(BLA-IV-52)**. Malonate **3.15i** was obtained in 71% yield (0.38 mmol scale) after 1 h in THF at room temperature (General Workup A) as a clear, colorless oil: ^{1}H NMR (400 MHz) δ 4.75 (d, *J* = 0.8 Hz, 1 H), 4.72 (d, *J* = 0.8 Hz, 1 H), 3.73 (s, 6 H), 3.62 (t, *J* = 8.0 Hz, 1 H), 2.62 (d, *J* = 7.6 Hz, 2 H), 1.74 (s, 3 H); ^{13}C NMR (100 MHz) δ 169.2, 141.3, 112.2, 52.5, 50.3, 36.6, 22.3; IR ($CDCl_3$) 2955, 2258, 1732, 1437, 1248, 1157 cm^{-1}; mass spectrum (CI) *m/z* 187.0976 [$C_{10}H_{17}O_4$ (M+1) requires 187.0970] 187, 155, 127 (base).

NMR Assignments: ^{1}H NMR (400 MHz) δ 4.75 (d, *J* = 0.8 Hz, 1 H, C1-H), 4.72 (d, *J* = 0.8 Hz, 1 H, C1-H), 3.73 (s, 6 H, C7-H), 3.62 (t, *J* = 8.0 Hz, 1 H, C4-H), 2.62 (d, *J* = 7.6 Hz, 2 H, C3-H), 1.74 (s, 3 H, C5-H); ^{13}C NMR (100 MHz) δ 169.2 (C6), 141.3 (C2), 112.2 (C1), 52.5 (C7), 50.3 (C3), 36.6 (C5), 22.3 (C4).

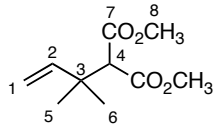


3.15j

2-(3-Methylbut-2-enyl)-malonic acid dimethyl ester (3.15j). **(BLA-IV-78)**. Malonate **3.15j** was obtained in 75% yield (0.34 mmol scale) after 12 h in DMF at -20 °C (General Workup C) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 92:8 regioisomeric ratio: ^{1}H NMR (400 MHz) δ 5.04 (app tt, *J* = 7.6, 1.2 Hz, 1 H), 3.73 (s, 6 H), 3.37 (t, *J* = 7.6 Hz, 1 H), 2.59 (app t, *J* = 7.6 Hz, 2 H), 1.68 (d, *J* = 1.2 Hz, 3

H), 1.63 (br s, 3 H); ^{13}C NMR (100 MHz) δ 169.3, 134.9, 119.3, 52.4, 51.9, 25.8, 17.8, 14.3; IR ($CDCl_3$) 2977, 2874, 2258, 1732, 1436, 1337, 1247, 1152, 1111, 1043 cm^{-1}; mass spectrum (CI) *m/z* 201.1125 [$C_{10}H_{17}O_4$ (M+1) requires 201.1127] 201 (base), 169.

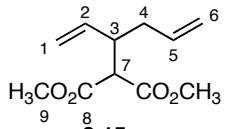
NMR Assignments: ^{1}H NMR (400 MHz) δ 5.04 (app tt, *J* = 7.6, 1.2 Hz, 1 H, C4-H), 3.73 (s, 6 H, C8-H), 3.37 (t, *J* = 7.6 Hz, 1 H, C6-H), 2.59 (app t, *J* = 7.6 Hz, 2 H, C5-H), 1.68 (d, *J* = 1.2 Hz, 3 H, C1-H), 1.63 (br s, 3 H, C2-H); ^{13}C NMR (100 MHz) δ 169.3 (C7), 134.9 (C3), 119.3 (C4), 52.4 (C8), 51.9 (C6), 25.8 (C1), 17.8 (C5), 14.3 (C2).



3.15l

2-(1,1-Dimethylallyl)-malonic acid dimethyl ester (3.15l). **(BLA-IV-92)**. Malonate **3.15l** was obtained in 80% yield (0.34 mmol scale) after 4 h in THF at 0 °C (General Workup A) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 94:6 regioisomeric ratio: ^{1}H NMR (400 MHz) δ 6.03 (dd, *J* = 17.2, 0.8 Hz, 1 H), 5.03 (dd, *J* = 17.2, 0.8 Hz, 1 H), 5.01 (dd, *J* = 11.2, 0.8 Hz, 1 H), 3.70 (s, 6 H), 3.37 (s, 1 H), 1.23 (s, 6 H); ^{13}C NMR (100 MHz) δ 168.0, 144.4, 112.2, 60.6, 52.0, 38.9, 25.2; IR ($CDCl_3$) 2954, 2873, 2258, 1733, 1436, 1329, 1247, 1144, 1031 cm^{-1}; mass spectrum (CI) *m/z* 201.1121 [$C_{10}H_{17}O_4$ (M+1) requires 201.1127] 201 (base), 169, 141.

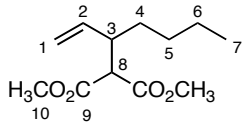
NMR Assignments: ^{1}H NMR (400 MHz) δ 6.03 (dd, *J* = 17.2, 0.8 Hz, 1 H, C2-H), 5.03 (dd, *J* = 17.2, 0.8 Hz, 1 H, C1-H), 5.01 (dd, *J* = 11.2, 0.8 Hz, 1 H, C1-H), 3.70 (s, 6 H, C8-H), 3.37 (s, 1 H, C4-H), 1.23 (s, 6 H, C5-C6-H); ^{13}C NMR (100 MHz) δ 168.0 (C7), 144.4 (C2), 112.2 (C1), 60.6 (C4), 52.0 (C8), 38.9 (C3), 25.2 (C5,C6).



3.15m

2-(1-Vinylbut-3-enyl)-malonic acid dimethyl ester (3.15m). **(BLA-IV-68)**. Malonate **3.15m** was obtained in 89% yield (0.32 mmol scale) after 1 h in THF at room temperature (General Workup A) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 91:9 regioisomeric ratio: ^{1}H NMR (400 MHz) δ 5.76-5.66 (m, 2 H), 5.10-4.99 (m, 4 H), 3.73 (s, 3 H), 3.69 (s, 3 H), 3.45 (d, *J* = 8.4 Hz, 1 H), 2.89 (app ddt, *J* = 14.0, 8.4, 4.8 Hz, 1 H), 2.27 (app dddt, *J* = 14.0, 8.4, 4.8, 0.8 Hz, 1 H), 2.16 (app dddt, *J* = 12.8, 8.0, 6.8, 0.8 Hz, 1 H); ^{13}C NMR (100 MHz) δ 168.4, 168.2, 137.3, 134.9, 117.2, 117.0, 55.7, 52.4, 52.3, 43.6, 36.9; IR ($CDCl_3$) 3081, 2954, 2845, 2258, 1732, 1436, 1251, 1195, 1151 cm^{-1}; mass spectrum (CI) *m/z* 213.1132 [$C_{11}H_{17}O_4$ (M+1) requires 213.1127] 213 (base), 181.

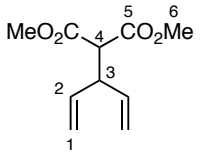
NMR Assignments: ^{1}H NMR (400 MHz) δ 5.76-5.66 (m, 2 H, C2-C5-H), 5.10-4.99 (m, 4 H, C1-C6-H), 3.73 (s, 3 H, C9-H), 3.69 (s, 3 H, C9-H), 3.45 (d, *J* = 8.4 Hz, 1 H, C7-H), 2.89 (app ddt, *J* = 14.0, 8.4, 4.8 Hz, 1 H, C4-H), 2.27 (app dddt, *J* = 14.0, 8.4, 4.8, 0.8 Hz, 1 H, C4-H), 2.16 (app dddt, *J* = 12.8, 8.0, 6.8, 0.8 Hz, 1 H, C3-H); ^{13}C NMR (100 MHz) δ 168.4 (C8), 168.2 (C8), 137.3 (C2), 134.9 (C5), 117.2 (C6), 117.0 (C1), 55.7 (C7), 52.4 (C9), 52.3 (C9), 43.6 (C4), 36.9 (C3).



3.15n

2-(1-Butylallyl)-malonic acid dimethyl ester (3.15n). **(BLA-IV-216)**. Malonate **3.15n** was obtained in 80% yield (0.20 mmol scale) after 4 h in THF at room temperature (General Workup A) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 57:43 regioisomeric ratio: ^{1}H NMR (400 MHz) 5.62 (ddd, *J* = 16.8, 10.0, 9.6 Hz, 1 H), 5.10-5.05 (comp, 2 H, C1-H), 3.73 (s, 3 H), 3.72 (s, 3 H), 3.38 (d, *J* = 8.4 Hz, 1 H), 2.75 (app ddt, *J* = 13.2, 9.2, 3.6 Hz, 1 H), 1.48-1.39 (m, 1 H), 1.33-1.16 (m, 5 H), 0.87 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz) 168.5, 168.3, 137.9, 117.3, 56.9, 52.2, 52.0, 32.0, 31.5, 22.5, 14.0; IR ($CDCl_3$) 2956, 2930, 2258, 1732, 1436, 1268, 1245, 1155 cm^{-1}; mass spectrum (CI) *m/z* 229.1446 [$C_{12}H_{21}O_4$ (M+1) requires 229.1440] 229 (base), 197, 169.

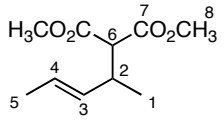
NMR Assignments: ^{1}H NMR (400 MHz) 5.62 (ddd, *J* = 16.8, 10.0, 9.6 Hz, 1 H, C2-H), 5.10-5.05 (comp, 2 H, C1-H), 3.73 (s, 3 H, C10-H), 3.72 (s, 3 H, C10-H), 3.38 (d, *J* = 8.4 Hz, 1 H, C8-H), 2.75 (app ddt, *J* = 13.2, 9.2, 3.6 Hz, 1 H, C3-H), 1.48-1.39 (m, 1 H, C4-H), 1.33-1.16 (m, 5 H, C4-C5-C6-H), 0.87 (t, *J* = 7.2 Hz, 3 H, C7-H); ^{13}C NMR (100 MHz) 168.5 (C9), 168.3 (C9), 137.9 (C2), 117.3 (C1), 56.9 (C8), 52.2 (C10), 52.0 (C10), 32.0 (C3), 32.0 (C4), 31.5 (C5), 22.5 (C6), 14.0 (C7).



3.15o

2-(1-Vinylallyl)-malonic acid dimethyl ester (3.15o) (BLA-V-116). Malonate **3.15o** was obtained in 74% yield (0.39 mmol scale) after 12 h in THF at 0 °C (General Workup A) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 96:4 regioisomeric ratio: ^{1}H NMR (400 MHz) δ 5.84-5.75 (m, 2 H), 5.15-5.09 (m, 4 H), 3.71 (s, 6 H), 3.53-3.49 (comp, 2 H); ^{13}C NMR (100 MHz) δ 168.0, 136.4, 117.1, 56.2, 52.4, 47.5; IR ($CHCl_3$) 3031, 2955, 1734, 1436, 1263, 1150, 1024, 928 cm^{-1}; mass spectrum (CI) *m/z* 199.0962 [$C_{10}H_{15}O_4$ (M+1) requires 199.0970] 199 (base), 65.

NMR Assignments: ^{1}H NMR (400 MHz) δ 5.84-5.75 (m, 2 H, C2-H), 5.15-5.09 (m, 4 H, C1-H), 3.71 (s, 6 H, C6-H), 3.53-3.49 (comp, 2 H, C3-C4-H); ^{13}C NMR (100 MHz) δ 168.0 (C5), 136.4 (C2), 117.1 (C1), 56.2 (C4), 52.4 (C6), 47.5 (C3).

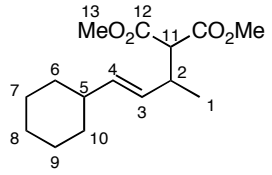


3.15p

2-(1-Methylbut-2-enyl)-malonic acid dimethyl ester (3.15p). (BLA-IV-85). Malonate **3.15p** was obtained in 89% yield (0.34 mmol scale) after 1 h in THF at room temperature and an additional 1 h at reflux (General Workup A) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1): ^{1}H NMR (400 MHz) δ 5.51 (ddd, *J* = 15.6, 6.5, 1.7 Hz, 1 H), 5.33 (ddq, *J* = 15.6, 8.4, 1.2 Hz, 1 H), 3.72 (s, 3 H), 3.69 (s, 3 H), 3.26

(d, *J* = 9.2 Hz, 1 H), 2.94-2.84 (m, 1 H), 1.63 (dd, *J* = 6.5, 1.7 Hz, 3 H), 1.06 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz) 168.6, 168.5, 132.0, 126.1, 57.9, 52.3, 52.2, 37.4, 18.6, 17.9; IR ($CHCl_3$) 3026, 2954, 1732, 1436, 1250, 1149 cm^{-1}; mass spectrum (CI) *m/z* 201.1123 [$C_{10}H_{17}O_4$ (M+1) requires 201.1127] 201 (base), 169.

NMR Assignments: ^{1}H NMR (400 MHz) 5.51 (ddd, *J* = 15.6, 6.5, 1.7 Hz, 1 H, C3-H), 5.33 (ddq, *J* = 15.6, 8.4, 1.2 Hz, 1 H, C4-H), 3.72 (s, 3 H, C8-H), 3.69 (s, 3 H, C8-H), 3.26 (d, *J* = 9.2 Hz, 1 H, C6-H), 2.94-2.84 (m, 1 H, C2-H), 1.63 (dd, *J* = 6.5, 1.7 Hz, 3 H, C5-H), 1.06 (d, *J* = 6.8 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz) 168.6 (C7), 168.5 (C7), 132.0 (C3), 126.1 (C4), 57.9 (C6), 52.3 (C8), 52.2 (C8), 37.4 (C2), 18.6 (C5), 17.9 (C1).

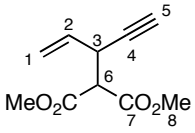


3.15r/3.16s

2-(3-Cyclohexyl-1-methylallyl)-malonic acid dimethyl ester (3.15r) (BLA-VI-104). Malonate **3.15r** was obtained in 94% yield (0.23 mmol scale) after 24 h in THF at 0 °C (General Workup B) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 93:7 regioisomeric ratio: ^{1}H NMR (400 MHz) 5.43 (dd, *J* = 15.6, 6.8 Hz, 1 H), 5.26 (ddd, *J* = 15.6, 8.4, 0.8 Hz, 1 H), 3.73 (s, 3 H), 3.68 (s, 3 H), 3.26 (d, *J* = 9.6 Hz, 1 H), 2.87 (ddq, *J* = 10.0, 9.6, 6.8 Hz, 1 H), 1.19-1.84 (m, 1 H), 1.71-1.61 (comp, 5 H), 1.28-0.99 (comp, 5 H), 1.05 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz) 168.8, 168.7, 137.8, 128.5, 58.2, 52.2, 52.1, 40.5, 37.6, 33.0, 32.9, 26.1, 25.9, 22.3, 18.7; IR ($CDCl_3$)

3692, 2927, 2852, 2257, 1732, 1602, 1436, 1250, 1196, 1153, 1022, 971 cm^{-1}; mass spectrum (CI) *m/z* 269.1765 [$C_{15}H_{25}O_4$ (M+1) requires 269.1753] 269 (base).

NMR Assignments: ^{1}H NMR (400 MHz) □ 5.43 (dd, *J* = 15.6, 6.8 Hz, 1 H, C3-H), 5.26 (ddd, *J* = 15.6, 8.4, 0.8 Hz, 1 H, C4-H), 3.73 (s, 3 H, C13-H), 3.68 (s, 3 H, C13-H), 3.26 (d, *J* = 9.6 Hz, 1 H, C11-H), 2.87 (ddq, *J* = 10.0, 9.6, 6.8 Hz, 1 H, C2-H), 1.19-1.84 (m, 1 H, C5-H), 1.71-1.61 (comp, 5 H, C6-C7-C8-C9-H_{eq}), 1.28-0.99 (comp, 5 H, C6-C7-C8-C9-H_{ax}), 1.05 (d, *J* = 6.8 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz) □ 168.8 (C12), 168.7 (C12), 137.8 (C3), 128.5 (C4), 58.2 (C11), 52.2 (C13), 52.1 (C13), 40.5 (C5), 37.6, 33.0, 32.9, 26.1, 25.9, 22.3, 18.7, (C1).



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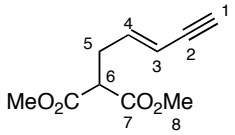
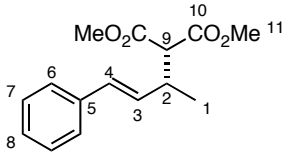


3.16

Dimethyl 2-(pent-1-en-4-yn-3-yl)malonate (3.15/3.16) (BLA-V-130). Malonates **3.15/3.16** were obtained in 91% yield (0.35 mmol scale) after –20 h in DMF at room temperature (General Workup B) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 53:47 regioisomeric ratio: **3.15** ^{1}H NMR (500 MHz) □ 5.83 (ddd, *J* = 18.0, 10.5, 6.5 Hz, 1 H), 5.44 (dt, *J* = 18.0, 1.0 Hz, 1 H), 5.22 (dt, *J* = 10.5, 1.0 Hz, 1 H), 3.89-3.85 (m, 1 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.57 (d, *J* = 9.0 Hz, 1 H), 2.29 (d, *J* = 2.5 Hz, 1 H); ^{13}C NMR (125 MHz) □ 167.4, 167.2, 133.2, 118.5, 80.9, 73.0, 56.6, 50.9, 32.0; **3.16:** ^{1}H NMR (500 MHz) □ 6.16 (dt, *J* = 16.0, 7.5 Hz, 1 H), 5.57 (ddt, *J* = 16.0, 2.0, 1.5 Hz, 1 H), 3.75 (s, 6 H), 3.45 (t, *J* = 7.5 Hz, 1 H), 2.83 (dd, *J* = 2.0, 0.5 Hz, 1

H), 2.70 (ddd, *J* = 9.0, 8.0, 0.5 Hz, 2 H); ^{13}C NMR (125 MHz) □ 168.8, 140.9, 111.9, 81.6, 77.1, 52.7, 52.7, 35.2; IR ($CDCl_3$) 3307, 1737, 1436, 1264, 1196, 1166, 1029, 988 cm^{-1}; mass spectrum (CI) *m/z* 197.0813 [$C_{10}H_{13}O_4$ (M+1) requires 197.0814] 197 (base).

NMR Assignments: 3.15: ^{1}H NMR (500 MHz) □ 5.83 (ddd, *J* = 18.0, 10.5, 6.5 Hz, 1 H, C2-H), 5.44 (dt, *J* = 18.0, 1.0 Hz, 1 H, C1-H), 5.22 (dt, *J* = 10.5, 1.0 Hz, 1 H, C1-H), 3.89-3.85 (m, 1 H, C3-H), 3.77 (s, 3 H, C8-H), 3.74 (s, 3 H, C8-H), 3.57 (d, *J* = 9.0 Hz, 1 H, C6-H), 2.29 (d, *J* = 2.5 Hz, 1 H, C5-H); ^{13}C NMR (125 MHz) □ 167.4 (C7), 167.2 (C7), 133.2 (C2), 118.5 (C1), 80.9 (C4), 73.0 (C5), 56.6 (C8), 50.9 (C8), 32.0 (C6); **3.16:** ^{1}H NMR (500 MHz) □ 6.16 (dt, *J* = 16.0, 7.5 Hz, 1 H, C2-H), 5.57 (ddt, *J* = 16.0, 2.0, 1.5 Hz, 1 H, C3-H), 3.75 (s, 6 H, C8-H), 3.45 (t, *J* = 7.5 Hz, 1 H, C6-H), 2.83 (dd, *J* = 2.0, 0.5 Hz, 1 H, C1-H), 2.70 (ddd, *J* = 9.0, 8.0, 0.5 Hz, 2 H, C5-H); ^{13}C NMR (125 MHz) □ 168.8 (C7), 140.9 (C3), 111.9 (C4), 81.6 (C2), 77.1 (C1), 52.7 (C8), 52.7 (C6), 35.2 (C5).

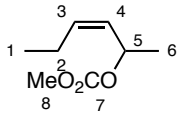


(+)-3.48

2-(1-Methyl-3-phenylallyl)-malonic acid dimethyl ester ((+)-4.48) (BLA-VI-116). Malonate **(+)-4.48** was obtained in 93% yield (0.24 mmol scale) after 24 h in DMF at room temperature (General Workup C) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 93:7 regioisomeric ratio: ^{1}H NMR (400 MHz) □ 7.34-7.26 (comp, 4 H), 7.21 (tt, *J* = 6.4, 1.2 Hz, 1 H), 6.45 (d, *J* = 15.7 Hz, 1 H), 6.12 (dd, *J* = 15.7, 8.5 Hz, 1 H), 3.75 (s, 3 H), 3.67 (s, 3 H), 3.40 (d, *J* = 8.9 Hz, 1 H), 3.17-3.08 (m, 1 H),

1.19 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz) δ 168.6, 168.5, 137.0, 131.1, 130.8, 128.4, 127.3, 126.2, 57.7, 52.4, 52.3, 37.7, 18.4; IR ($CDCl_3$) 3692, 2955, 2257, 1733, 1601, 1436, 1249, 1195, 1165 cm^{-1}; mass spectrum (CI) m/z 263.1284 [$C_{15}H_{19}O_4$ (M+1) requires 263.1283] 263 (base), 131; HPLC (Chiracel AD column, hexanes/isopropanol = 98:2, flow = 0.5 mL/min) $^{24}[a]_D$ = +38.1° (c = 1.0, $CHCl_3$).

NMR Assignments: ^{1}H NMR (400 MHz) δ 7.34-7.26 (comp, 4 H, C6-C7-H), 7.21 (tt, J = 6.4, 1.2 Hz, 1 H, C8-H), 6.45 (d, J = 15.7 Hz, 1 H, C4-H), 6.12 (dd, J = 15.7, 8.5 Hz, 1 H, C3-H), 3.75 (s, 3 H, C11-H), 3.67 (s, 3 H, C11-H), 3.40 (d, J = 8.9 Hz, 1 H, C9-H), 3.17-3.08 (m, 1 H, C2-H), 1.19 (d, J = 6.8 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz) δ 168.6 (C10), 168.5 (C10), 137.0 (C5), 131.1, 130.8, 128.4, 127.3, 126.2, 57.7 (C9), 52.4 (C11), 52.3 (C11), 37.7 (C2), 18.4 (C1).

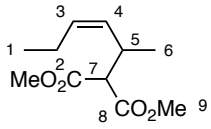


3.70

(*Z*)-hex-3-en-2-yl methyl carbonate (3.70) (BLA-VI-187). Hex-3-yn-2-ol (**3.68**) (500 mg, 5.09 mmol) was added to a slurry of Lindlar's catalyst (25 mg) and quinoline (24 μL, 0.20 mmol) in EtOAc (2.5 mL) at room temperature. The reaction flask was then flushed with H_2, and the slurry was stirred vigorously under an atmosphere of H_2 (balloon) for 3 h. The mixture was filtered through celite, the filter cake was washed with EtOAc (50 mL), and the combined filtrate and washings were concentrated under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C, whereupon pyridine (1.21 g, 1.24 mL, 15.3 mmol) and methyl chloroformate (1.44 g,

1.20 mL, 15.3 mmol) were added sequentially. The cooling bath was removed, and the resulting solution was stirred for 2 h at room temperature. Saturated aqueous NaCl (20 mL) was added, and the layers separated. The aqueous layer was extracted with Et_2O (3 x 20 mL), and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to provide 459 mg (57%) of **3.70** as a clear, colorless oil: ^{1}H NMR (400 MHz) δ 5.56-5.47 (comp, 2 H), 5.36 (ddt, *J* = 10.8, 8.8, 1.6 Hz, 1 H), 3.76 (s, 3 H), 2.23-2.09 (m, 1 H), 1.34 (d, *J* = 6.8 Hz, 3 H), 1.00 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz) δ 155.0, 135.0, 128.0, 70.9, 54.3, 20.9, 20.7, 14.0; IR ($CHCl_3$) 3024, 2983, 1746, 1443, 1345, 1319, 1272, 1170, 1051, 943, 867 cm^{-1}.

NMR Assignments: ^{1}H NMR (400 MHz) δ 5.56-5.47 (comp, 2 H, C4-C5-H), 5.36 (ddt, *J* = 10.8, 8.8, 1.6 Hz, 1 H, C3-H), 3.76 (s, 3 H, C8-H), 2.23-2.09 (m, 1 H, C2-H), 1.34 (d, *J* = 6.8 Hz, 3 H, C6-H), 1.00 (t, *J* = 7.6 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz) δ 155.0 (C7), 135.0 (C4), 128.0 (C3), 70.9 (C5), 54.3 (C8), 20.9 (C2), 20.7 (C6), 14.0 (C1).

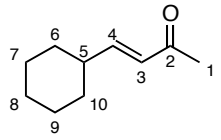


3.71

(*Z*)-dimethyl 2-(hex-3-en-2-yl)malonate (3.71) (BLA-VI-265). Malonate **3.71** was obtained after 24 h in THF at room temperature (General Workup B) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a >95:5 regioisomeric ratio

and cis/trans ratio of 75:25: ***cis*-isomer:** ^{1}H NMR (400 MHz) 5.38 (dt, *J* = 11.2, 7.2 Hz, 1 H), 5.19-5.13 (m, 1 H), 3.74 (s, 3 H), 3.68 (s, 3 H), 3.26-3.24 (m, 1 H), 2.16-2.03 (m, 2 H), 1.04 (d, *J* = 6.4 Hz, 3 H), 0.96 (d, *J* = 7.6 Hz, 3 H). ***trans*-isomer:** ^{1}H NMR (400 MHz) 5.54 (dt, *J* = 15.6, 5.6 Hz, 1 H), 5.31 (ddt, *J* = 15.6, 8.8, 1.2 Hz, 1 H), 3.73 (s, 3 H), 3.67 (s, 3 H); ^{13}C NMR (100 MHz) 168.8, 132.9, 130.2, 57.9, 53.4, 32.5, 25.1, 19.2, 14.3; IR ($CDCl_3$) 2955, 2258, 1754, 1732, 1436, 1265, 1196, 1144 cm^{-1}; mass spectrum (CI) *m/z* 215.1290 [$C_{11}H_{19}O_4$ (M+1) requires 215.1283] 215 (base), 201.

NMR Assignments: *cis*-isomer: ^{1}H NMR (400 MHz) 5.38 (dt, *J* = 11.2, 7.2 Hz, 1 H, C4-H), 5.19-5.13 (m, 1 H, C3-H), 3.74 (s, 3 H, C9-H), 3.68 (s, 3 H, C11-H), 3.26-3.24 (m, 1 H, C5-C7-H), 2.16-2.03 (m, 2 H, C2-H), 1.04 (d, *J* = 6.4 Hz, 3 H, C6-H), 0.96 (d, *J* = 7.6 Hz, 3 H, C1-H). ***trans*-isomer:** ^{1}H NMR (400 MHz) 5.54 (dt, *J* = 15.6, 5.6 Hz, 1 H, C4-H), 5.31 (ddt, *J* = 15.6, 8.8, 1.2 Hz, 1 H, C3-H), 3.73 (s, 3 H, C9-H), 3.67 (s, 3 H, C11-H).

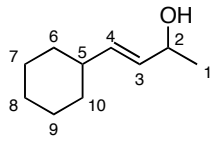


3.27

4-Cyclohexyl but-3-en-2-one (3.27). (BLA-VI-95). Diethyl (2-oxopropyl)-phosphonate (495 mg, 0.5 mL, 2.54 mmol) was added to a slurry of NaH (97 mg of a 60% mineral oil suspension, 2.4 mmol) in THF (6.4 mL) at 0 ˚C, and stirred for 1 h. Cyclohexyl carboxaldehyde (**3.26**) (143 mg, 0.15 mL, 1.29 mmol) was then added dropwise, the cooling bath was removed, and the resulting solution stirred for an additional 1.5 h at room temperature. H_2O (5 mL) was added and the layers were

separated. The aqueous phase was extracted with Et_2O (3 x 5 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to give 182 mg (94%) of **3.27** as a clear, colorless oil: ^{1}H NMR (400 MHz) 6.73 (dd, *J* = 16.0, 6.8 Hz, 1 H), 6.02 (dd, *J* = 16.0, 1.2 Hz, 1 H), 2.25 (s, 3 H), 2.17-2.11 (m, 1 H), 1.79-1.67 (comp, 5 H), 1.36-1.11 (comp, 5 H); ^{13}C NMR (100 MHz) 198.9, 153.2, 128.6, 40.4, 31.6, 26.7, 25.7, 25.5; IR ($CHCl_3$) 3016, 2930, 2854, 1669, 1621, 1450, 1359, 1265, 980 cm^{-1}; mass spectrum (CI) *m/z* 153.1270 [$C_{10}H_{17}O_1$ (M+1) requires 153.1279] 305, 185, 153 (base), 65.

NMR Assignments: ^{1}H NMR (400 MHz) 6.73 (dd, *J* = 16.0, 6.8 Hz, 1 H, C4-H), 6.02 (dd, *J* = 16.0, 1.2 Hz, 1 H, C3-H), 2.25 (s, 3 H, C1-H), 2.17-2.11 (m, 1 H, C5-H), 1.79-1.67 (comp, 5 H, C6-C7-C8-C9-H_{eq}), 1.36-1.11 (comp, 5 H, C6-C7-C8-C9-H_{ax}); ^{13}C NMR (100 MHz) 198.9 (C2), 153.2 (C4), 128.6 (C3), 40.4 (C5), 31.6 (C6,C10), 26.7 (C8), 25.7 (C7,C9), 25.5 (C1).

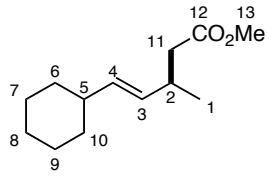


3.28

4-Cyclohexyl but-3-en-2-ol (3.28). (BLA-VI-98). Enone **3.27** (100 mg, 0.65 mmol) was added to a slurry of $LiAlH_4$ (25 mg, 0.65 mmol) in Et_2O (6 mL) at 0 ˚C and the resulting mixture was stirred for 1 h. Saturated aqueous NH_4Cl (5 mL) was added and the reaction allowed to warm to room temperature by removal of the cooling bath. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 5 mL).

The combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure to afford 93 mg (94%) of **3.28** as a clear, colorless oil: ^{1}H NMR (400 MHz) 5.58 (ddd, *J* = 15.2, 6.4, 0.8 Hz, 1 H), 5.46 (ddd, *J* = 15.2, 6.4, 1.2 Hz, 1 H), 4.24 (app dq, *J* = 6.8, 6.0 Hz, 1 H), 1.97-1.89 (m, 1 H), 1.75-1.62 (comp, 5 H), 1.38 (s, 1 H), 1.32-1.01 (comp, 5 H), 1.25 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz) 136.7, 131.5, 68.9, 40.1, 32.8, 32.7, 26.0, 25.9, 23.4; IR ($CDCl_3$) 3692, 3606, 2927, 2853, 2250, 1602, 1449, 1374, 1250, 1044, 972 cm^{-1}; mass spectrum (CI) *m/z* 155.1431 [$C_{10}H_{19}O$ (M+1) requires 155.1436] 155, 153, 137 (base).

NMR Assignments: ^{1}H NMR (400 MHz) 5.58 (ddd, *J* = 15.2, 6.4, 0.8 Hz, 1 H, C3-H) 5.46 (ddd, *J* = 15.2, 6.4, 1.2 Hz, 1 H, C4-H), 4.24 (app dq, *J* = 6.8, 6.0 Hz, 1 H, C2-H), 1.97-1.89 (m, 1 H, C5-H), 1.75-1.62 (comp, 5 H, C6-C7-C8-C9-C10-H$_{eq}$), 1.38 (s, 1 H, O-H), 1.32-1.01 (comp, 5 H, C6-C7-C8-C9-C10-H$_{ax}$), 1.25 (d, *J* = 6.0 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz) 136.7 (C4), 131.5 (C3), 68.9 (C2), 40.1 (C5), 32.8, 32.7, 26.0, 25.9, 23.4 (C1).

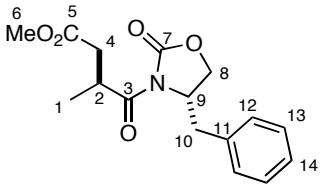


3.49

5-Cyclohexyl-3-methyl pent-4-enoic acid methyl ester (3.49) (BLA-V-244). H_2O (1 drop) was added to a solution of malonate **(+)-3.16s** (47 mg, 0.18 mmol) and NaCl (21 mg, 0.35 mmol) in DMSO (2 mL) at room temperature. The reaction was immersed in an oil bath preheated to 140 °C (bath temperature), and the mixture stirred for 24 h. The reaction was allowed to cool to room temperature, H_2O (50 mL) was

added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to give **3.49** as a clear, colorless oil: ^{1}H NMR (400 MHz) δ 5.37 (dd, *J* = 15.4, 6.2 Hz, 1 H), 5.27 (ddd, *J* = 15.4, 7.2, 1.0 Hz, 1 H), 3.64 (s, 3 H), 2.64-2.57 (m, 1 H), 2.29 (dd, *J* = 14.5, 7.2 Hz, 1 H), 2.24 (dd, *J* = 14.5, 7.4 Hz, 1 H), 1.91-1.84 (m, 1 H), 1.71-1.59 (comp, 5 H), 1.29-0.98 (comp, 5 H), 1.01 (d, *J* = 6.8, 3 H); ^{13}C NMR (100 MHz) δ 173.2, 135.6, 131.4, 51.3, 42.0, 40.6, 33.8, 33.2, 26.2, 26.1, 20.5; IR ($CHCl_3$) 2926, 2852, 1731, 1436, 1350, 1287, 1208, 1171, 970 cm^{-1}; mass spectrum (CI) *m/z* 211.1692[$C_{13}H_{23}O_2$ (M+1) requires 211.1698] 211 (base).

NMR Assignments: ^{1}H NMR (400 MHz) δ 5.37 (dd, *J* = 15.4, 6.2 Hz, 1 H, C4-H), 5.27 (ddd, *J* = 15.4, 7.2, 1.0 Hz, 1 H, C3-H), 3.64 (s, 3 H, C13-H), 2.64-2.57 (m, 1 H, C2-H), 2.29 (dd, *J* = 14.5, 7.2 Hz, 1 H, C11-H), 2.24 (dd, *J* = 14.5, 7.4 Hz, 1 H, C11-H), 1.91-1.84 (m, 1 H, C5-H), 1.71-1.59 (comp, 5 H, C6-C7-C8-C9-C10-H_{eq}), 1.29-0.98 (comp, 5 H, C6-C7-C8-C9-C10-H_{ax}), 1.01 (d, *J* = 6.8 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz) δ 173.2 (C12), 135.6 (C3), 131.4 (C4), 51.3 (C13), 42.0 (C11), 40.6 (C5), 33.8, 33.2, 26.2, 26.1, 20.5 (C1).

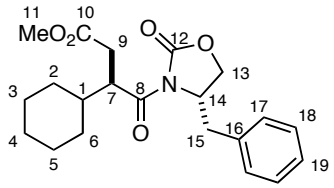


3.54

(3*R*)-4-[(4*R*)-4-Benzyl-2-oxo-oxazolidin-3-yl]-3-methyl-4-oxobutyric acid methyl ester (3.54). (BLA-VI-93). NaHMDS (1.29 mL, 1.0 M in THF) was added to a solution of imide **3.53** (200 mg, 0.85 mmol) in THF (9 mL) at –78 ˚C, and the resulting solution was stirred for 1.5 h. Methyl bromoacetate (262 mg, 0.16 mL, 1.7 mmol) was then added dropwise at –78 ˚C, the cooling bath was removed, and the reaction stirred at room temperature for 24 h. Saturated aqueous NH_4Cl (10 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexane/EtOAc (2:1) to give 182 mg (71%) of **3.54** as a clear, colorless oil: ^{1}H NMR (400 MHz) □ 7.36-7.32 (comp, 2 H), 7.29-7.25 (comp, 3 H), 4.68 (app ddt, *J* = 9.6, 7.2, 3.6 Hz, 1 H), 4.22-4.15 (comp, 3 H), 3.67 (s, 3 H), 3.33 (dd, *J* = 13.2, 3.6 Hz, 1 H), 2.95 (dd, *J* = 16.8, 10.4 Hz, 1 H), 2.76 (dd, *J* = 13.2, 10.4 Hz, 1 H), 2.47 (dd, *J* = 16.8, 4.4 Hz, 1 H), 1.23 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz) □ 175.9, 172.2, 152.9, 135.4, 129.4, 128.8, 127.2, 65.9, 55.3, 51.7, 37.5, 37.4, 34.4, 17.2; IR ($CHCl_3$) 3022, 1781, 1734, 1698, 1455, 1439, 1390, 1353, 1264, 1108, 1075, 1053, 1016, 974, 909 cm^{-1}; mass spectrum (CI) *m/z* 306.1350 [$C_{16}H_{20}NO_5$ (M+1) requires 306.1341] 306 (base), 129.

NMR Assignments: ^{1}H NMR (400 MHz) □ 7.36-7.32 (comp, 2 H, C_{AR}-H), 7.29-7.25 (comp, 3 H, C_{AR}-H), 4.68 (app ddt, *J* = 9.6, 7.2, 3.6 Hz, 1 H, C8-H), 4.22-4.15 (comp, 3 H, C9-C2-H), 3.67 (s, 3 H, C6-H), 3.33 (dd, *J* = 13.2, 3.6 Hz, 1 H, C10-H), 2.95

(dd, *J* = 16.8, 10.4 Hz, 1 H, C4-H), 2.76 (dd, *J* = 13.2, 10.4 Hz, 1 H, C10-H), 2.47 (dd, *J* = 16.8, 4.4 Hz, 1 H, C4-H), 1.23 (d, *J* = 6.8 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz) 175.9 (C3), 172.2 (C5), 152.9 (C7), 135.4 (C11), 129.4, 128.8, 127.2, 65.9 (C9), 55.3 (C6), 51.7 (C8), 37.5, 37.4, 34.4 (C2), 17.2 (C1).

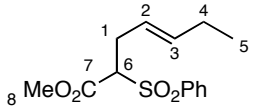


3.54a

(3*R*)-4-[(4*R*)-4-Benzyl-2-oxo-oxazolidin-3-yl]-3-cyclohexyl-4-oxo-butyric acid methyl ester (3.54a) (BLA-V-244). NaHMDS (2.49 mL, 1.0 M in THF) was added to a solution of imide **3.53a** (500 mg, 1.65 mmol) in THF (8 mL) at –78 ˚C, and the resulting solution was stirred for 1 h. Methyl bromoacetate (761 mg, 0.47 mL, 4.98 mmol) was then added dropwise at –78 ˚C, the cooling bath was removed, and the reaction was stirred at room temperature for 18 h. Saturated aqueous NH_4Cl (10 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexane/EtOAc (5:1) to give 534 mg (87%) of **3.54a** as a clear, colorless oil: ^{1}H NMR (400 MHz) 7.35-7.32 (comp, 2 H), 7.28-7.20 (comp, 3 H), 4.70-4.65 (m, 1 H), 4.22-4.12 (comp, 3 H), 3.65 (s, 3 H), 3.36 (dd, *J* = 13.2, 3.2 Hz, 1 H), 2.92 (dd, *J* = 17.2, 12.0 Hz, 1 H), 2.73 (dd, *J* = 13.6, 10.4 Hz, 1 H), 2.58 (dd, *J* = 17.2, 3.6 Hz, 1 H), 1.93-1.88

(m, 1 H), 1.76-1.58 (comp, 5 H), 1.33-0.96 (comp, 5 H); ^{13}C NMR (100 MHz) □ 175.2, 172.9, 153.0, 135.7, 129.4, 128.7, 127.0, 65.6, 55.6, 51.7, 43.8, 39.8, 37.2, 32.8, 30.7, 28.9, 26.3, 26.2, 26.0; IR ($CHCl_3$) 3025, 2931, 2856, 1780, 1733, 1693, 1450, 1386, 1350, 1236, 1196, 1103, 1017, 909 cm^{-1}; mass spectrum (CI) *m/z* 374.1957[$C_{21}H_{28}NO_5$ (M+1) requires 374.1967] 374 (base).

NMR Assignments: ^{1}H NMR (400 MHz) □ 7.35-7.32 (comp, 2 H), 7.28-7.20 (comp, 3 H), 4.70-4.65 (m, 1 H, C13-H), 4.22-4.12 (comp, 3 H, C14-C7-H), 3.65 (s, 3 H, C11-H), 3.36 (dd, *J* = 13.2, 3.2 Hz, 1 H, C15-H), 2.92 (dd, *J* = 17.2, 12.0 Hz, 1 H, C9-H), 2.73 (dd, *J* = 13.6, 10.4 Hz, 1 H, C15-H), 2.58 (dd, *J* = 17.2, 3.6 Hz, 1 H, C9-H), 1.93-1.88 (m, 1 H, C1-H), 1.76-1.58 (comp, 5 H, C2-C3-C4-C5-C6-H_{eq}), 1.33-0.96 (comp, 5 H, C2-C3-C4-C5-C6-H_{ax}); ^{13}C NMR (100 MHz) □ 175.2 (C8), 172.9 (C10), 153.0 (C12), 135.7 (16), 129.4, 128.7, 127.0, 65.6 (C14), 55.6 (C11), 51.7 (C13), 43.8 (C15), 39.8 (C7), 37.2 (C9), 32.8 (C1), 30.7, 28.9, 26.3, 26.2, 26.0.



3.73

2-Benzenesulfonyl hept-4-enoic acid methyl ester (3.73). (BLA-VI-23). $[Rh(CO)_2Cl]_2$ (7 mg, 17.0 □mol) was dissolved in degassed THF (1.5 mL), **3.14a** (50 mg, 0.34 mmol) was added, and the solution stirred for 30 min at room temperature. In a separate flask, methyl phenylsulfonylacetate **3.72** (0.15 mL, 0.87 mmol) was added to a slurry of NaH (28 mg of a 60% mineral oil suspension, 0.69 mmol) in degassed THF (2.0 mL) at room temperature and stirred for 20 min. The resulting anion was added *via* syringe to the solution of **3.14a** and $[Rh(CO)_2Cl]_2$ at room temperature and stirred for 4 h.

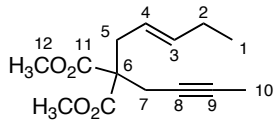
The resulting dark brown solution was then filtered through a short plug of silica gel eluting with Et_2O (50 mL) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to give 72 mg (75%) of **3.73** in a ≥ 95:5 regioisomeric ratio as a clear, colorless oil: ^{1}H NMR (400 MHz) δ 7.91-7.87 (m, 2 H), 7.72-7.67 (m, 1 H), 7.61-7.56 (m, 2 H), 5.56 (app dt, *J* = 15.4, 6.1 Hz, 1 H), 5.22 (app dddt, *J* = 15.4, 8.8, 7.6, 1.2 Hz, 1 H), 3.97 (dd, *J* = 11.3, 3.8 Hz, 1 H), 3.66 (s, 3 H), 2.77-2.69 (m, 1 H), 2.60 (dddd, *J* = 19.2, 11.6, 7.6, 0.8 Hz, 1 H), 1.95 (dq, *J* = 14.0, 6.4 Hz, 2 H), 0.91 (app t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz) δ 165.9, 137.2, 136.9, 134.3, 129.2, 129.0, 121.6, 70.6, 52.7, 29.9, 25.4, 13.4; IR ($CHCl_3$) 3021, 2965, 1742, 1448, 1327, 1265, 1150, 1084, 969, 909 cm^{-1}; mass spectrum (CI) *m*/*z* 283.1009 [$C_{14}H_{19}O_4S$ (M+1) requires 283.1004] 315, 283 (base).

NMR Assignments: ^{1}H NMR (400 MHz) δ 7.91-7.87 (m, 2 H, C_{Ar}-H), 7.72-7.67 (m, 1 H, C12-H, C_{Ar}-H), 7.61-7.56 (m, 1 H, C_{Ar}-H), 5.56 (app dt, *J* = 15.4, 6.1 Hz, 1 H, C2-H), 5.22 (app dddt, *J* = 15.4, 8.8, 7.6, 1.2 Hz, 1 H, C3-H), 3.97 (dd, *J* = 11.3, 3.8 Hz, 1 H, C6-H), 3.66 (s, 3 H, C8-H), 2.77-2.69 (m, 1 H, C1-H), 2.60 (dddd, *J* = 19.2, 11.6, 7.6, 0.8 Hz, 1 H, C1-H), 1.95 (dq, *J* = 14.0, 6.4 Hz, 2 H, C4-H), 0.91 (app t, *J* = 7.6 Hz, 3 H, C5-H); ^{13}C NMR (100 MHz) δ 165.9 (C7), 137.2, 136.9, 134.3, 129.2, 129.0, 121.6, 70.6 (C6), 52.7 (C8), 29.9 (C4), 25.4 (C1), 13.4 (C5).

From 3.14e. (BLA-VI-222). $[Rh(CO)_2Cl]_2$ (13 mg, 34 μmol) was dissolved in degassed THF (2 mL), **3.14e** (mmol) was added, and the solution stirred for 30 min. In a separate flask, methyl phenylsulfonylacetate (186 mg, 0.87 mmol) was added to a slurry of NaH (28 mg of a 60% mineral oil suspension, 0.69 mmol) in degassed THF (1.5 mL) at room temperature, and stirred for 20 min. The resulting enolate was added via syringe to the solution of **3.14e** and $[Rh(CO)_2Cl]_2$ at room temperature and stirred for 4 h. The resulting dark brown solution was then filtered through a short plug of silica gel eluting

with Et_2O (50 mL) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to give 73 mg (76%) of **3.73** in >95:5 regioselectivity and *Z*/*E* = 1:1.5 as a clear, colorless oil whose spectral characterization was equal in all respects to that reported previously.

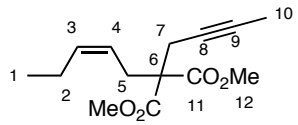
General procedure for the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation of unsymmetrical allylic carbonates with dimethyl 2-(but-2-ynyl)malonate. $[Rh(CO)_2Cl]_2$ (19.0 mg, 10 mol %) was dissolved in the indicated degassed solvent (5 mL), **3.14** (1.0 mmol) was added, and the solution stirred for 10-15 min. In a separate flask, dimethyl 2-(but-2-ynyl)malonate (276 mg, 1.5 mmol) was added to a slurry of NaH (56 mg of a 60% mineral oil suspension, 1.4 mmol) in the indicated degassed solvent (5 mL) and stirred for 20 min at room temperature. The resulting malonate anion was added *via* syringe to the solution of allylic substrate and $[Rh(CO)_2Cl]_2$ at room temperature. The mixture was then stirred for the indicated time at the indicated temperature. **General Workup A:** Saturated aqueous $NaHCO_3$ (10 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. **General Workup B:** The reaction was filtered through a short plug of silica gel eluting with Et_2O (50 mL) and was concentrated under reduced pressure. **General Workup C:** Saturated aqueous NH_4Cl (10 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic fractions were washed with saturated aqueous NaCl (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography to provide the alkylation products **3.89/3.90** in the specified ratio.



3.89a

2-But-2-ynyl-2-pent-2-enylmalonic acid dimethyl ester (3.89a). **(BLA-V-25)**. Malonate **3.89a** was obtained in 95% yield (0.13 mmol scale) after 2 h in THF at room temperature (General Workup A) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 94:6 regioisomeric ratio: ^{1}H NMR (500 MHz) □ 5.59 (dddt, *J* = 15.2, 7.6, 6.5, 1.1 Hz, 1 H), 5.22 (dddt, *J* = 15.2, 9.0, 7.5, 1.6 Hz, 1 H), 3.72 (s, 6 H), 2.74-2.70 (m, 4 H), 1.99 (ddq, *J* = 9.0, 7.5, 1.1 Hz, 2 H), 1.76 (t, *J* = 2.5 Hz, 3 H), 0.94 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz) □ 170.7, 137.5, 122.0, 78.7, 73.4, 57.6, 52.5, 35.3, 25.6, 22.9, 13.7, 3.5; IR ($CHCl_3$) 3027, 2956, 1732, 1438, 1283, 1228, 1202, 1068, 971 cm^{-1}; mass spectrum (CI) *m/z* 253.1434 [$C_{14}H_{21}O_4$ (M+1) requires 253.1440] 253 (base), 221, 194, 133.

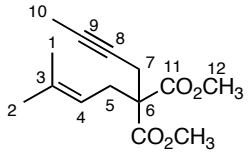
NMR Assignments: ^{1}H NMR (400 MHz) □ 5.59 (dddt, *J* = 15.2, 7.6, 6.5, 1.1 Hz, 1 H, C4-H), 5.22 (dddt, *J* = 15.2, 9.0, 7.5, 1.6 Hz, 1 H, C3-H), 3.72 (s, 6 H, C12-H), 2.74-2.70 (m, 4 H, C5-C7-H), 1.99 (ddq, *J* = 9.0, 7.5, 1.1 Hz, 2 H, C2-H), 1.76 (t, *J* = 2.5 Hz, 3 H, C10-H), 0.94 (t, *J* = 7.5 Hz, 3 H, C1-H); ^{13}C NMR (125 MHz) □ 170.7 (C11), 137.5 (C3), 122.0 (C4), 78.7 (C9), 73.4 (C8), 57.6 (C6), 52.5 (C12), 35.3 (C5), 25.6 (C2), 22.9 (C7), 13.7 (C1), 3.5 (C10).



3.89b

(*Z*)-dimethyl 2-(but-2-ynyl)-2-(pent-2-enyl)malonate (3.89b). **(BLA-VII-179)**. Malonate **3.89b** was obtained in 94% yield (0.34 mmol scale) after 12 h in THF at –20 °C (General Workup A) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a >95:5 regioisomeric ratio and a mixture (88:12) of *Z*/*E*-isomers: ^{1}H NMR (400 MHz) 5.54 (dtt, *J* = 10.8, 8.8, 2.0 Hz, 1 H), 5.11 (dtt, *J* = 10.8, 9.2, 2.0 Hz, 1 H), 3.76 (s, 6 H), 2.81 (dd, *J* = 8.0, 1.6 Hz, 2 H), 2.73 (q, *J* = 2.4 Hz, 2 H), 2.09 (ddq, *J* = 9.2, 7.2, 1.6 Hz, 2 H), 1.75 (t, *J* = 2.8 Hz, 3 H), 0.96 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz) 170.6, 136.3, 121.4, 78.6, 73.4, 57.1, 52.6, 29.7, 22.8, 20.5, 14.1, 3.4; IR ($CDCl_3$) 3690, 2956, 2359, 1733, 1601, 1437, 1294, 1247, 1215, 1054 cm^{-1}; mass spectrum (CI) *m*/*z* 253.1446 [$C_{14}H_{21}O_4$ (M+1) requires 253.1440] 253 (base), 221, 193.

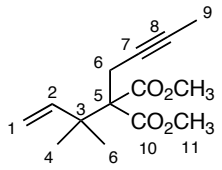
NMR Assignments: ^{1}H NMR (400 MHz) 5.54 (dtt, *J* = 10.8, 8.8, 2.0 Hz, 1 H, C3-H), 5.11 (dtt, *J* = 10.8, 9.2, 2.0 Hz, 1 H, C4-H), 3.76 (s, 6 H, C12-H), 2.81 (dd, *J* = 8.0, 1.6 Hz, 2 H, C5-H), 2.73 (q, *J* = 2.4 Hz, 2 H, C7-H), 2.09 (ddq, *J* = 9.2, 7.2, 1.6 Hz, 2 H, C2-H), 1.75 (t, *J* = 2.8 Hz, 3 H, C10-H), 0.96 (t, *J* = 7.6 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz) 170.6 (C11), 136.3 (C4), 121.4 (C3), 78.6 (C8), 73.4 (C9), 57.1 (C12), 52.6 (C6), 29.7 (C5), 22.8 (C7), 20.5 (C2), 14.1 (C1), 3.4 (C10).



3.89c

2-But-2-ynyl-2-(3-methylbut-2-enyl)malonic acid dimethyl ester (3.89c). (BLA-V-26). Malonate **3.89c** was obtained in 85% yield (0.14 mmol scale) after 20 h in DMF at –20 ˚C (General Workup B) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 99:1 regioisomeric ratio: ^{1}H NMR (400 MHz) □ 4.91 (dt, *J* = 7.6, 1.6 Hz, 1 H), 3.72 (s, 6 H), 2.75 (d, *J* = 7.6 Hz, 2 H), 2.71 (q, *J* = 2.4 Hz, 2 H), 1.75 (t, *J* = 2.4 Hz, 3 H), 1.69 (d, *J* = 1.6 Hz, 3 H), 1.65 (d, *J* = 1.6 Hz, 3 H); ^{13}C NMR (100 MHz) □ 170.8, 136.5, 117.2, 77.8, 73.7, 57.4, 52.6, 30.7, 26.0, 22.8, 17.8, 3.5; IR ($CDCl_3$) 2954, 2922, 2359, 2258, 1732, 1437, 1264, 1227, 1207, 1058 cm^{-1}; mass spectrum (CI) *m/z* 253.1436 [$C_{14}H_{21}O_4$ (M+1) requires 253.1440] 253, 221, 193 (base), 185, 151.

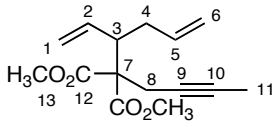
NMR Assignments: ^{1}H NMR (400 MHz) □ 4.91 (dt, *J* = 7.6, 1.6 Hz, 1 H, C4-H), 3.72 (s, 6 H, C12-H), 2.75 (d, *J* = 7.6 Hz, 2 H, C5-H), 2.71 (q, *J* = 2.4 Hz, 2 H, C7-H), 1.75 (t, *J* = 2.4 Hz, 3 H, C10-H), 1.69 (d, *J* = 1.6 Hz, 3 H, C2-H), 1.65 (d, *J* = 1.6 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz) □ 170.8 (C11), 136.5 (C3), 117.2 (C4), 77.8 (C8), 73.7 (C9), 57.4 (C6), 52.6 (C12), 30.7 (C2), 26.0 (C5), 22.8 (C1), 17.8 (C7), 3.5 (C10).



3.89d

2-But-2-ynyl-2-(1,1-dimethyl-allyl)-malonic acid dimethyl ester (3.89d). (BLA-IV-183). Malonate **3.89d** was obtained in 82% yield (0.34 mmol scale) after 20 h in DMF at –20 ˚C (General Workup B) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 57:43 regioisomeric ratio: ^{1}H NMR (400 MHz) δ 6.16 (dd, *J* = 17.6, 11.2 Hz, 1 H), 5.03 (dd, *J* = 11.2, 1.2 Hz, 1 H), 5.01 (dd, *J* = 17.6, 1.2 Hz, 1 H), 3.74 (s, 6 H), 2.72 (q, *J* = 2.4 Hz, 2 H), 1.73 (t, *J* = 2.4 Hz, 3 H), 1.25 (s, 6 H); ^{13}C NMR (100 MHz) δ 170.2, 144.1, 112.9, 77.8, 73.7, 64.1, 52.0, 41.9, 23.9, 17.8, 3.5; IR ($CDCl_3$) 2953, 2922, 2259, 1731, 1436, 1294, 1227, 1207, 1070 cm^{-1}; mass spectrum (CI) *m/z* 253.1433 [$C_{14}H_{21}O_4$ (M+1) requires 253.1440] 253, 193 (base), 185.

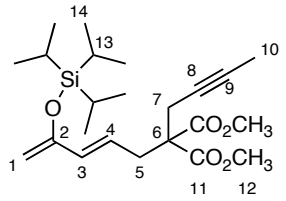
NMR Assignments: ^{1}H NMR (400 MHz) δ 6.16 (dd, *J* = 17.6, 11.2 Hz, 1 H, C2-H), 5.03 (dd, *J* = 11.2, 1.2 Hz, 1 H, C1-H), 5.01 (dd, *J* = 17.6, 1.2 Hz, 1 H, C1-H), 3.74 (s, 6 H, C11-H), 2.72 (q, *J* = 2.4 Hz, 2 H, C6-H), 1.73 (t, *J* = 2.4 Hz, 3 H, C9-H), 1.25 (s, 6 H, C4-H); ^{13}C NMR (100 MHz) δ 170.2 (C10), 144.1 (C2), 112.9 (C1), 77.8 (C7), 73.7 (C8), 64.1 (C3), 52.0 (C11), 41.9 (C5), 23.9 (C4), 17.8 (C6), 3.5 (C9).



3.89e

2-But-2-ynyl-2-(1-vinylbut-3-enyl)-malonic acid dimethyl ester (3.89e). **(BLA-V-27)**. Malonate **3.89e** was obtained in 74% yield (0.13 mmol scale) after 2 h in THF at room temperature (General Workup A) as a clear, colorless oil after chromatography (hexanes/EtOAc = 5:1) in a 93:7 regioisomeric ratio: ^{1}H NMR (500 MHz) □ 5.83-5.67 (m, 1 H), 5.51 (app dt, *J* = 16.8, 10.0 Hz, 1 H), 5.17-4.97 (comp, 4 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 2.90 (app dt, *J* = 11.2, 2.8 Hz, 1 H), 2.73 (q, *J* = 2.8 Hz, 2 H), 2.59 (ddddd, *J* = 14.0, 5.2, 2.8, 1.2, 1.2 Hz, 1 H), 1.99-1.91 (m, 1 H), 1.76 (t, *J* = 2.8 Hz, 3 H); ^{13}C NMR (125 MHz) □ 170.6, 170.1, 136.9, 135.9, 118.9, 115.9, 78.8, 73.7, 60.2, 52.4, 52.3, 47.3, 35.1, 24.4, 3.5; IR ($CDCl_3$) 2954, 2922, 2844, 2359, 2259, 1731, 1437, 1219, 1051 cm^{-1} mass spectrum (CI) *m/z* 265.1443 [$C_{15}H_{21}O_4$ (M+1) requires 265.1440] 265 (base), 233, 205, 145.

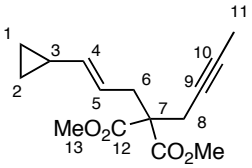
NMR Assignments: ^{1}H NMR (500 MHz) □ 5.83-5.67 (m, 1 H, C5-H), 5.51 (app dt, *J* = 16.8, 10.0 Hz, 1 H, C2-H), 5.17-4.97 (comp, 4 H, C1-C6-H), 3.75 (s, 3 H, C13-H), 3.74 (s, 3 H, C13-H), 2.90 (app dt, *J* = 11.2, 2.8 Hz, 1 H, C3-H), 2.73 (q, *J* = 2.8 Hz, 2 H, C8-H), 2.59 (ddddd, *J* = 14.0, 5.2, 2.8, 1.2, 1.2 Hz, 1 H, C4-H), 1.99-1.91 (m, 1 H, C4-H), 1.76 (t, *J* = 2.8 Hz, 3 H, C11-H); ^{13}C NMR (125 MHz) □ 170.6 (C12), 170.1 (C12), 136.9 (C2), 135.9 (C5), 118.9 (C6), 115.9 (C1), 78.8 (C9), 73.7 (C10), 60.2 (C7), 52.4 (C13), 52.3 (C13), 47.3 (C3), 35.1 (C4), 24.4 (C8), 3.5 (C11).



3.89f

2-But-2-ynyl-2-[4-(triisopropylsilanyloxy)-penta-2,4-dienyl]malonic acid dimethyl ester (3.89f). **(BLA-IV-188)**. Malonate **3.89f** was obtained in 35% yield (0.06 mmol scale) after 24 h in THF at room temperature (General Workup A) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a >95:5 regioisomeric ratio: ^{1}H NMR (500 MHz) □ 5.98 (d, *J* = 15.1 Hz, 1 H), 5.85 (dt, *J* = 15.1, 7.6 Hz, 1 H), 4.26 (s, 1 H), 4.21 (s, 1 H), 3.72 (s, 6 H), 2.84 (dd, *J* = 7.6, 0.6 Hz, 2 H), 2.72 (q, *J* = 2.4 Hz, 2 H), 1.76 (t, *J* = 2.4 Hz, 3 H), 1.21 (sept, *J* = 7.8 Hz, 3 H), 1.09 (d, *J* = 7.8 Hz, 18 H); ^{13}C NMR (125 MHz) □ 170.4, 154.7, 132.3, 124.2, 94.3, 78.9, 73.3, 57.4, 52.6, 34.9, 23.1, 18.0, 12.7, 3.5; IR ($CHCl_3$) 2956, 2867, 1736, 1438, 1258, 1206, 1094, 1069, 1024, 982 cm^{-1}; mass spectrum (CI) *m/z* 423.2557 [$C_{23}H_{39}O_5Si$ (M+1) requires 423.2567] 423 (base).

NMR Assignments: ^{1}H NMR (400 MHz) □ 5.98 (d, *J* = 15.1 Hz, 1 H, C3-H), 5.85 (dt, *J* = 15.1, 7.6 Hz, 1 H, C4-H), 4.26 (s, 1 H, C1-H), 4.21 (s, 1 H, C1-H), 3.72 (s, 6 H, C12-H), 2.84 (dd, *J* = 7.6, 0.6 Hz, 2 H, C5-H), 2.72 (q, *J* = 2.4 Hz, 2 H, C7-H), 1.76 (t, *J* = 2.4 Hz, 3 H, C10-H), 1.21 (sept, *J* = 7.8 Hz, 3 H, C13-H), 1.09 (d, *J* = 7.8 Hz, 18 H, C14-H); ^{13}C NMR (100 MHz) □ 170.4 (C11), 154.7 (C2), 132.3 (C3), 124.2 (C4), 94.3 (C1), 78.9 (C9), 73.3 (C8), 57.4 (C6), 52.6 (C12), 34.9 (C5), 23.1 (C7), 18.0 (C14), 12.7 (C13), 3.5 (C10).



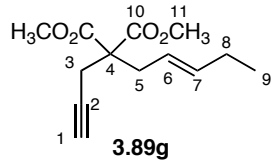
3.151

2-But-2-ynyl-2-(3-cyclopropyl-allyl)-malonic acid dimethyl ester (3.151). (BLA-V-110). Malonate **3.151** was obtained in 63% yield (0.13 mmol scale) after 1.5 h in THF at room temperature (General Workup B) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a >95:5 regioisomeric ratio: ^{1}H NMR (500 MHz) 5.29 (app dt, *J* = 15.1, 7.5 Hz, 1 H), 5.10 (dd, *J* = 15.1, 9.0 Hz, 1 H), 3.72 (s, 6 H), 2.73 (app q, *J* = 5.0, 2.5 Hz, 2 H), 1.75 (app t, *J* = 2.5 Hz, 3 H), 1.33 (app ddt, *J* = 13.1, 8.5, 4.8 Hz, 1 H), 0.66 (dddd, *J* = 8.0, 6.0, 4.5, 4.5 Hz, 2 H), 0.31 (app dt, *J* = 6.5, 4.5 Hz, 2 H); ^{13}C NMR (125 MHz) 170.7, 139.3, 120.5, 78.7, 73.5, 57.6, 52.5, 35.3, 22.9, 13.6, 6.6, 3.5; mass spectrum (CI) *m/z* 265.1451 [$C_{15}H_{21}O_4$ (M+1) requires 265.1440] 265, 205 (base).

NMR Assignments: ^{1}H NMR (500 MHz) 5.29 (app dt, *J* = 15.1, 7.5 Hz, 1 H, C5-H), 5.10 (dd, *J* = 15.1, 9.0 Hz, 1 H, C4-H), 3.72 (s, 6 H, C13-H), 2.73 (app q, *J* = 5.0, 2.5 Hz, 2 H, C8-H), 2.70 (dd, *J* = 7.5, 1.0 Hz, 2 H, C6-H), 1.75 (app t, *J* = 2.5 Hz, 3 H, C11-H), 1.33 (app ddt, *J* = 13.1, 8.5, 4.8 Hz, 1 H, C3-H), 0.66 (dddd, *J* = 8.0, 6.0, 4.5, 4.5 Hz, 2 H, C1-C2-H), 0.31 (app dt, *J* = 6.5, 4.5 Hz, 2 H, C1-C2-H); ^{13}C NMR (125 MHz) 170.7 (C12), 139.3 (C4), 120.5 (C5), 78.7 (C9), 73.5 (C10), 57.6 (C7), 52.5 (C13), 35.3 (C6), 22.9 (C8), 13.6 (C3), 6.6 (C1,C2), 3.5 (C11).

General procedure for the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation of unsymmetrical allylic carbonates with dimethyl 2-(prop-2-ynyl)malonate.

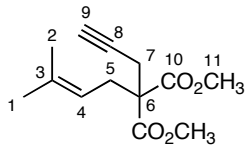
$[Rh(CO)_2Cl]_2$ (19.0 mg, 10 mol%) was dissolved in the indicated degassed solvent (5 mL), **3.14** (1.0 mmol) was added and the solution stirred for 10-15 min. In a separate flask, dimethyl 2-(prop-2-ynyl)malonate (255 mg, 1.5 mmol) was added to a slurry of NaH (56 mg of a 60% mineral oil suspension, 1.4 mmol) in the indicated degassed solvent (5 mL) and was stirred for 20 min at room temperature. The resulting malonate anion was added *via* syringe to the solution of allylic substrate and $[Rh(CO)_2Cl]_2$ at room temperature. The mixture was then stirred for the indicated time at the indicated temperature. **General Workup A:** Saturated aqueous $NaHCO_3$ (10 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. **General Workup B:** The reaction was filtered through a short plug of silica gel eluting with Et_2O (50 mL) and the combined filtrates were concentrated under reduced pressure. **General Workup C:** Saturated aqueous NH_4Cl (10 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic fractions were washed with saturated aqueous NaCl (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography to provide the alkylation products **3.89/3.90** in the specified ratio.



3.89g

***trans*-2-Pent-2-enylmalonic acid dimethyl ester (3.89g). (BLA-III-292).** Malonate **3.89g** was obtained in 75% yield (0.34 mmol scale) after 6 h in THF at room temperature (General Workup A) as a clear, colorless oil after chromatography (hexanes/EtOAc = 5:1) in a 98:2 regioisomeric ratio: ^{1}H NMR (400 MHz) 5.62 (dtt, *J* = 14.8, 7.6, 0.8 Hz, 1 H), 5.19 (dtt, *J* = 15.2, 7.6, 1.2 Hz, 1 H), 3.73 (s, 3 H), 2.78 (d, *J* = 2.8 Hz, 2 H), 2.73 (dd, *J* = 7.6, 1.2 Hz, 2 H), 2.04-1.96 (m, 3 H), 0.95 (t, *J* = 2.8 Hz, 3 H); ^{13}C NMR (100 MHz) 170.0, 137.7, 121.5, 78.9, 71.3, 57.2, 52.7, 35.3, 25.8, 22.7, 13.8; IR ($CDCl_3$) 3308, 2956, 2259, 1734, 1438, 1283, 1213 cm^{-1}; mass spectrum (CI) *m*/*z* 239.1280 [$C_{13}H_{19}O_4$ (M+1) requires 239.1283] 239 (base), 207, 179.

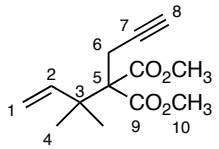
NMR Assignments: ^{1}H NMR (400 MHz) 5.62 (dtt, *J* = 14.8, 7.6, 0.8 Hz, 1 H, C6-H), 5.19 (dtt, *J* = 15.2, 7.6, 1.2 Hz, 1 H, C7-H), 3.73 (s, 3 H, C11-H), 2.78 (d, *J* = 2.8 Hz, 2 H, C3-H), 2.73 (dd, *J* = 7.6, 1.2 Hz, 2 H, C5-H), 2.04-1.96 (m, 3 H, C1-C8-H), 0.95 (t, *J* = 2.8 Hz, 3 H, C9-H); ^{13}C NMR (100 MHz) 170.0 (C10), 137.7 (C6), 121.5 (C7), 78.9 (C2), 71.3 (C1), 57.2 (C4), 52.7 (C11), 35.3 (C3), 25.8 (C5), 22.7 (C8), 13.8 (C9).



3.89h

2-(3-Methylbut-2-enyl)-2-prop-2-ynylmalonic acid dimethyl ester (3.89h). (BLA-V-42). Malonate **3.89h** was obtained in 70% yield (0.34 mmol scale) after 12 h in DMF at –20 ˚C (General Workup B) as a clear, colorless oil after chromatography (hexanes/EtOAc = 5:1) in a 99:1 regioisomeric ratio: ^{1}H NMR (400 MHz) □ 4.90 (tt, *J* = 7.9, 1.4 Hz, 1 H), 3.73 (s, 6 H), 2.79-2.78 (m, 4 H), 2.00 (t, *J* = 2.4 Hz, 1 H), 1.70 (d, *J* = 1.0 Hz, 3 H), 1.65 (s, 3 H); ^{13}C NMR (100 MHz) □ 170.5, 136.9, 116.9, 79.2, 71.2, 57.1, 52.7, 30.7, 26.0, 22.5, 17.9; IR ($CDCl_3$) 3308, 2955, 2259, 1733, 1437 cm^{-1}; mass spectrum (CI) *m/z* 239.1283 [$C_{13}H_{19}O_4$ (M+1) requires 239.1283] 239 (base), 207.

NMR Assignments: ^{1}H NMR (400 MHz) □ 4.90 (tt, *J* = 7.9, 1.4 Hz, 1 H, C4-H), 3.73 (s, 6 H, C11-H), 2.79-2.78 (m, 4 H, C5-C7-H), 2.00 (t, *J* = 2.4 Hz, 1 H, C9-H), 1.70 (d, *J* = 1.0 Hz, 3 H, C2-H), 1.65 (s, 3 H, C1-H); ^{13}C NMR (100 MHz) □ 170.5 (C10), 136.9 (C7), 116.9 (C6), 79.2 (C2), 71.2 (C1), 57.1 (C4), 52.7 (C11), 30.7 (C9), 26.0 (C5), 22.5 (C8), 17.9 (C3).

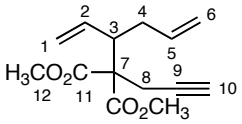


3.89i

2-(1,1-Dimethylallyl)-2-prop-2-ynylmalonic acid dimethyl ester (3.89i). (BLA-IV-159). Malonate **3.89i** was obtained in 98% yield (0.34 mmol scale) after 24 h in DMF

at –20 ˚C (General Workup B) as a clear, colorless oil after chromatography (hexanes/EtOAc = 5:1) in a 88:12 regioisomeric ratio: ^{1}H NMR (400 MHz) δ 6.15 (dd, *J* = 17.2, 10.8 Hz, 1 H), 5.04 (dd, *J* = 10.8, 1.2 Hz, 1 H), 5.03 (dd, *J* = 17.2, 1.2 Hz, 1 H), 3.75 (s, 6 H), 2.80 (d, *J* = 2.8 Hz, 2 H), 1.98 (t, *J* = 2.8 Hz, 1 H), 1.25 (s, 6 H); ^{13}C NMR (100 MHz) δ 169.9, 143.7, 113.3, 81.0, 70.4, 63.9, 52.1, 42.0, 23.9, 23.1; IR ($CDCl_3$) 3308, 2953, 2258, 1730, 1435, 1264, 1206, 1068 cm^{-1}; mass spectrum (CI) *m/z* 239.1285 [$C_{13}H_{19}O_4$ (M+1) requires 239.1283] 239, 179, 171 (base), 147, 139.

NMR Assignments: ^{1}H NMR (400 MHz) δ 6.15 (dd, *J* = 17.2, 10.8 Hz, 1 H, C2-H), 5.04 (dd, *J* = 10.8, 1.2 Hz, 1 H, C1-H), 5.03 (dd, *J* = 17.2, 1.2 Hz, 1 H, C1-H), 3.75 (s, 6 H, C10-H), 2.80 (d, *J* = 2.8 Hz, 2 H, C6-H), 1.98 (t, *J* = 2.8 Hz, 1 H, C8-H), 1.25 (s, 6 H, C4-H); ^{13}C NMR (100 MHz) δ 169.9 (C9), 143.7 (C2), 113.3 (C1), 81.0 (C7), 70.4 (C8), 63.9 (C5), 52.1 (C10), 42.0 (C3), 23.9 (C4), 23.1 (C6).



3.89j

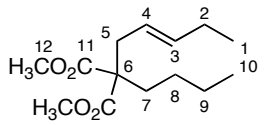
2-Prop-2-ynyl-2-(1-vinylbut-3-enyl)-malonic acid dimethyl ester (3.89j). (BLA-V-48). Malonate **3.89j** was obtained in 71% yield (0.32 mmol scale) after 1.5 h in THF at room temperature (General Workup B) as a clear, colorless oil after chromatography (hexanes/EtOAc = 5:1) in a 93:7 regioisomeric ratio: ^{1}H NMR (400 MHz) δ 5.65-5.58 (m, 1 H), 5.30-5.23 (m, 1 H), 5.05-4.98 (comp, 4 H), 3.76 (s, 3 H), 3.76 (s, 3 H), 2.83-2.73 (comp, 5 H), 2.02 (t, *J* = 2.4 Hz, 2 H); ^{13}C NMR (100 MHz) δ 170.2, 136.5, 133.4, 124.1, 115.3, 78.8, 71.4, 57.0, 52.3, 36.6, 35.3, 22.6; IR ($CDCl_3$)

3308, 2954, 2844, 2259, 1733, 1639, 1437, 1289, 1208, 1072 cm^{-1}; mass spectrum (CI) *m/z* 251.1281 [$C_{14}H_{19}O_4$ (M+1) requires 251.1283] 251 (base), 219, 191.

NMR Assignments: 5.65-5.58 (m, 1 H), 5.30-5.23 (m, 1 H), 5.05-4.98 (comp, 4 H, C1-C6-H), 3.76 (s, 3 H, C12-H), 3.76 (s, 3 H, C12-H), 2.83-2.73 (comp, 5 H, C4-C3-C8-H), 2.02 (t, *J* = 2.4 Hz, 2 H, C10-H); ^{13}C NMR (100 MHz) □ 170.2 (C11), 136.5, 133.4, 124.1, 115.3, 78.8 (C10), 71.4 (C9), 57.0 (C7), 52.3 (C12), 36.6, 35.3, 22.6.

General procedure for the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation of unsymmetrical allylic carbonates with dimethyl 2-butylmalonate. $[Rh(CO)_2Cl]_2$ (19.0 mg, 10 mol%) was dissolved in the indicated degassed solvent (5 mL), **3.14** (1.0 mmol) was added and the solution stirred for 10-15 min. In a separate flask, dimethyl 2-butylmalonate (282 mg, 1.5 mmol) was added to a slurry of NaH (56 mg of a 60% mineral oil suspension, 1.4 mmol) in the indicated degassed solvent (5 mL) at room temperature, and the mixture was stirred for 20 min at room temperature. The resulting malonate anion was added *via* syringe to the solution of allylic substrate and $[Rh(CO)_2Cl]_2$ at room temperature. The mixture was then stirred for the indicated time at the indicated temperature. **General Workup A:** Saturated aqueous $NaHCO_3$ (10 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. **General Workup B:** The reaction was filtered through a short plug of silica gel eluting with Et_2O (50 mL) and the combined filtrates were concentrated under reduced pressure. **General Workup C:** Saturated aqueous NH_4Cl (10 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic fractions were washed with saturated aqueous NaCl (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was

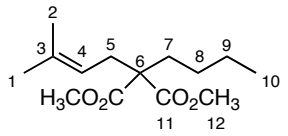
purified by flash chromatography to provide the alkylation products **3.89/3.90** in the specified ratio.



3.89k

2-Butyl-2-pent-2-enylmalonic acid dimethyl ester (3.89k). (BLA-IV-304). Malonate **3.89k** was obtained in 91% yield (0.34 mmol scale) after 3 h in THF at room temperature and an additional 4 h at 70 ˚C (bath temperature) (General Workup A) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 91:9 regioisomeric ratio: ^{1}H NMR (400 MHz) □ 5.52 (dtt, *J* = 15.2, 6.4, 1.2 Hz, 1 H), 5.22 (dtt, *J* = 15.2, 7.2, 1.2 Hz, 1 H), 3.70 (s, 3 H), 2.57 (dd, *J* = 7.2, 1.2 Hz, 2 H), 2.01-1.83 (m, 4 H), 1.35-1.27 (m, 2 H), 1.17-1.09 (m, 2 H), 0.94 (t, *J* = 7.2 Hz, 3 H), 0.89 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz) □ 171.9, 136.7, 122.5, 57.8, 52.1, 35.7, 31.9, 26.0, 25.6, 22.8, 13.8, 13.7; IR ($CDCl_3$) 2958, 2873, 2258, 1727, 1456, 1435, 1270, 1210, 1145, 1044, 970 cm^{-1}; mass spectrum (CI) *m/z* 257.1751 [$C_{14}H_{25}O_4$ (M+1) requires 257.1753] 257 (base), 196, 168.

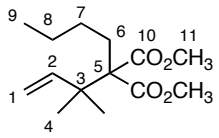
NMR Assignments: ^{1}H NMR (400 MHz) □ 5.52 (dtt, *J* = 15.2, 6.4, 1.2 Hz, 1 H, C3-H), 5.22 (dtt, *J* = 15.2, 7.2, 1.2 Hz, 1 H, C4-H), 3.70 (s, 3 H, C12-H), 2.57 (dd, *J* = 7.2, 1.2 Hz, 2 H, C5-H), 2.01-1.83 (m, 4 H, C2-C7-H), 1.35-1.27 (m, 2 H, C9-H), 1.17-1.09 (m, 2 H, C8-H), 0.94 (t, *J* = 7.2 Hz, 3 H, C1-H), 0.89 (t, *J* = 7.2 Hz, 3 H, C10-H); ^{13}C NMR (100 MHz) □ 171.9 (C11), 136.7 (C4), 122.5 (C3), 57.8 (C6), 52.1 (C12), 35.7 (C5), 31.9 (C7), 26.0 (C2), 25.6 (C8), 22.8 (C9), 13.8 (C1), 13.7 (C10).



3.89l

2-Butyl-2-(3-methylbut-2-enyl)malonic acid dimethyl ester (3.89l). **(BLA-IV-183)**. Malonate **3.89l** was obtained in 88% yield (0.34 mmol scale) after 12 h in DMF at -20 ˚C (General Workup B) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 99:1 regioisomeric ratio: ^{1}H NMR (400 MHz) 4.93 (app ddt, *J* = 8.8, 7.2, 1.2 Hz, 1 H), 3.70 (s, 3 H), 2.60 (d, *J* = 7.2 Hz, 2 H), 1.85 (dd, *J* = 9.2, 7.2 Hz, 2 H), 1.69 (d, *J* = 0.8 Hz, 3 H), 1.61 (br s, 3 H), 1.34-1.26 (m, 2 H), 1.16-1.08 (m, 2 H), 0.89 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz) 172.1, 135.4, 117.7, 57.6, 52.2, 31.9, 31.0, 26.2, 25.9, 22.9, 17.8, 13.8; IR ($CDCl_3$) 2956, 2874, 2259, 1728, 1435, 1209, 1128, 1052 cm^{-1}; mass spectrum (CI) *m/z* 257.1758 [$C_{14}H_{25}O_4$ (M+1) requires 257.1753] 257 (base), 196.

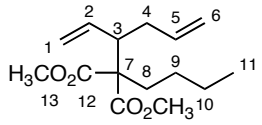
NMR Assignments: ^{1}H NMR (400 MHz) 4.93 (app ddt, *J* = 8.8, 7.2, 1.2 Hz, 1 H, C4-H), 3.70 (s, 3 H, C12-H), 2.60 (d, *J* = 7.2 Hz, 2 H, C5-H), 1.85 (dd, *J* = 9.2, 7.2 Hz, 2 H, C7-H), 1.69 (d, *J* = 0.8 Hz, 3 H, C1-H), 1.61 (br s, 3 H, C2-H), 1.34-1.26 (m, 2 H, C9-H), 1.16-1.08 (m, 2 H, C8-H), 0.89 (t, *J* = 7.2 Hz, 3 H, C10-H); ^{13}C NMR (100 MHz) 172.1 (C11), 135.4 (C3), 117.7 (C4), 57.6 (C6), 52.2 (C12), 31.9 (C7), 31.0 (C8), 26.2 (C2), 25.9 (C5), 22.9 (C9), 17.8 (C1), 13.8 (C10).



3.89m

2-Butyl-2-(1,1-dimethylallyl)-malonic acid dimethyl ester (3.89m). **(BLA-V-45)**. Malonate **3.89m** was obtained in 62% yield (0.34 mmol scale) after 12 h in DMF at -20 ˚C (General Workup B) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1) in a 93:7 regioisomeric ratio: ^{1}H NMR (400 MHz) δ 6.17 (dd, *J* = 17.6, 11.2 Hz, 1 H), 5.01 (dd, *J* = 11.2, 1.2 Hz, 1 H), 4.98 (dd, *J* = 17.6, 1.2 Hz, 1 H), 3.74 (s, 6 H), 1.85 (t, *J* = 8.4 Hz, 2 H), 1.30 (tq, *J* = 14.0, 7.2 Hz, 2 H), 1.19 (s, 6 H), 1.16-1.10 (m, 2 H), 0.88 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz) δ 171.3, 144.5, 112.4, 64.7, 52.4, 32.2, 28.5, 25.9, 24.0, 22.9, 13.8; IR ($CDCl_3$) 2956, 2873, 2259, 1728, 1456, 1435, 1278, 1209, 1127, 1054, 1018 cm^{-1}; mass spectrum (CI) *m/z* 257.1749 [$C_{14}H_{25}O_4$ (M+1) requires 257.1753] 257 (base), 225, 196, 157.

NMR Assignments: ^{1}H NMR (400 MHz) δ 6.17 (dd, *J* = 17.6, 11.2 Hz, 1 H, C2-H), 5.01 (dd, *J* = 11.2, 1.2 Hz, 1 H, C1-H), 4.98 (dd, *J* = 17.6, 1.2 Hz, 1 H, C1-H), 3.74 (s, 6 H, C11-H), 1.85 (t, *J* = 8.4 Hz, 2 H, C6-H), 1.30 (tq, *J* = 14.0, 7.2 Hz, 2 H, C8-H), 1.19 (s, 6 H, C4-H), 1.16-1.10 (m, 2 H, C7-H), 0.88 (t, *J* = 7.2 Hz, 3 H, C9-H); ^{13}C NMR (100 MHz) δ 171.3 (C10), 144.5 (C2), 112.4 (C1), 64.7 (C5), 52.4 (C11), 32.2 (C3), 28.5 (C7), 25.9 (C6), 24.0 (C8), 22.9 (C4), 13.8 (C9).



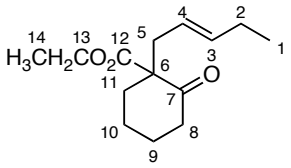
3.89n

2-Butyl-2-(1-vinylbut-3-enyl)-malonic acid dimethyl ester (3.89n). **(BLA-V-23)**. Malonate **3.89n** was obtained in 71% yield (0.32 mmol scale) after 3 h in THF at room temperature and an additional 4 h at 70 ˚C (General Workup A) as a clear, colorless oil after chromatography (pentane/Et_2O = 5:1): ^{1}H NMR (400 MHz) 5.69 (app ddt, *J* = 16.8, 10.0, 7.2 Hz, 1 H), 5.54 (dt, *J* = 16.4, 9.6 Hz, 1 H), 5.13 (dd, *J* = 10.0, 1.6 Hz, 1 H), 5.04-4.96 (comp, 3 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 2.71-2.63 (comp, 2 H), 2.45 (dddd, *J* = 14.0, 6.8, 1.2, 1.2 Hz, 1 H), 1.89-1.83 (comp, 2 H), 1.34-1.24 (comp, 4 H), 0.87 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz) 171.9, 171.5, 136.4, 134.2, 118.3, 115.9, 60.9, 52.0, 51.9, 35.3, 34.1, 26.4, 26.1, 22.9, 13.8; IR ($CDCl_3$) 2956, 2863, 2359, 1726, 1601, 1435, 1267, 1210, 1127, 992 cm^{-1}; mass spectrum (CI) *m/z* 269.1762 [$C_{15}H_{25}O_4$ (M+1) requires 269.1753] 269 (base), 238, 209.

NMR Assignments: ^{1}H NMR (400 MHz) 5.69 (app ddt, *J* = 16.8, 10.0, 7.2 Hz, 1 H, C12-H), 5.54 (dt, *J* = 16.4, 9.6 Hz, 1 H, C12-H), 5.13 (dd, *J* = 10.0, 1.6 Hz, 1 H), 5.04-4.96 (comp, 3 H), 3.74 (s, 3 H, C13-H), 3.72 (s, 3 H, C13-H), 2.71-2.63 (comp, 2 H, C3-C4-H), 2.45 (dddd, *J* = 14.0, 6.8, 1.2, 1.2 Hz, 1 H, C4-H), 1.89-1.83 (comp, 2 H), 1.34-1.24 (comp, 4 H), 0.87 (t, *J* = 7.2 Hz, 3 H, C11-H); ^{13}C NMR (100 MHz) 171.9 (C12), 171.5 (C12), 136.4 (C2), 134.2 (C5), 118.3 (C1), 115.9 (C6), 60.9 (C7), 52.0 (C13), 51.9 (C13), 35.3 (C3), 34.1 (C4), 26.4 (C8), 26.1 (C9), 22.9 (C10), 13.8 (C11).

General procedure for the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation of unsymmetrical allylic carbonates with ethyl 2-oxocyclohexanecarboxylate.

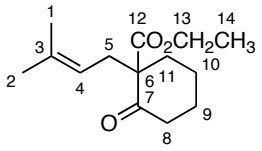
$[Rh(CO)_2Cl]_2$ (19.0 mg, 10 mol%) was dissolved in the indicated degassed solvent (5 mL), **3.14** (1.0 mmol) was added and the solution stirred for 10-15 min. In a separate flask, ethyl 2-oxocyclohexanecarboxylate (255 mg, 1.5 mmol) was added to a slurry of NaH (56 mg of a 60% mineral oil suspension, 1.4 mmol) in the indicated degassed solvent (5 mL) and stirred for 20 min at room temperature. The resulting malonate anion was added *via* syringe to the solution of allylic substrate and $[Rh(CO)_2Cl]_2$ at room temperature. The mixture was then stirred for the indicated time at the indicated temperature. **General Workup A:** The resulting dark brown solution was diluted with saturated aqueous $NaHCO_3$ (10 mL), the layers were separated, and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. **General Workup B:** The reaction was filtered through a short plug of silica gel eluting with Et_2O (50 mL). The combined filtrate and washings were then concentrated under reduced pressure. **General Workup C:** The resulting dark brown solution was then diluted with saturated aqueous NH_4Cl (10 mL), the layers were separated, and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with saturated aqueous NaCl (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography to provide the alkylation product **3.97** with the specified regioselectivity.



3.97a

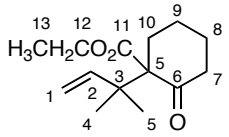
2-Oxo-1-pent-2-enyl-cyclohexanecarboxylic acid ethyl ester (3.97a). (BLA-V-37). -Ketoester **3.97a** was obtained in 98% yield (0.34 mmol scale) in THF after 4 h at room temperature (General Workup B) as a clear, colorless oil after chromatography (hexanes/EtOAc = 5:1) in a 95:5 regioisomeric ratio: ^{1}H NMR (400 MHz) 5.47 (dt, *J* = 15.4, 6.2 Hz, 1 H), 5.33 (dt, *J* = 15.4, 7.9 Hz, 1 H), 4.17 (q, *J* = 7.5 Hz, 2 H), 2.55 (dd, *J* = 14.0, 6.8 Hz, 1 H), 2.45 (dd, *J* = 6.2, 3.1 Hz, 2 H), 2.25 (dd, *J* = 14.3, 7.5 Hz, 1 H), 2.03-1.94 (m, 1 H), 1.99 (app pent, *J* = 7.5 Hz, 2 H), 1.74-1.65 (m, 4 H), 1.47-1.40 (m, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 0.94 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz) 207.8, 171.5, 136.0, 123.4, 61.2, 61.0, 41.1, 38.0, 35.7, 27.5, 25.5, 22.4, 14.2, 13.7; IR ($CDCl_3$) 2941, 2358, 1709, 1219, 1200 cm^{-1}; mass spectrum (CI) *m/z* 239.1641 [$C_{14}H_{23}O_3$ (M+1) requires 239.1647] 239 (base), 193, 171, 165.

NMR Assignments: ^{1}H NMR (400 MHz) 5.47 (dt, *J* = 15.4, 6.2 Hz, 1 H, C4-H), 5.33 (dt, *J* = 15.4, 7.9 Hz, 1 H, C3-H), 4.17 (q, *J* = 7.5 Hz, 2 H, C13-H), 2.55 (dd, *J* = 14.0, 6.8 Hz, 1 H, C8-H), 2.45 (dd, *J* = 6.2, 3.1 Hz, 2 H, C5-H), 2.25 (dd, *J* = 14.3, 7.5 Hz, 1 H, C8-H), 2.03-1.94 (m, 1 H, C11-H), 1.99 (app pent, *J* = 7.5 Hz, 2 H, C2-H), 1.74-1.65 (m, 4 H, C9-C10-H), 1.47-1.40 (m, 1 H, C11-H), 1.25 (t, *J* = 7.2 Hz, 3 H, C14-H), 0.94 (t, *J* = 7.5 Hz, 3 H, C1-H); ^{13}C NMR (100 MHz) 207.8 (C7), 171.5 (C12), 136.0 (C4), 123.4 (C3), 61.2 (C6), 61.0 (C13), 41.1 (C8), 38.0 (C5), 35.7 (C11), 27.5 (C10), 25.5 (C2), 22.4 (C9), 14.2 (C1), 13.7 (C14).



3.97b

1-(3-Methylbut-2-enyl)-2-oxocyclohexanecarboxylic acid ethyl ester (3.97b). (BLA-V-38). -Ketoester **3.97b** was obtained in 86% yield (0.34 mmol scale) in THF after 6 h at room temperature (General Workup B) as a clear, colorless oil after chromatography (hexanes/EtOAc = 5:1) in a 99:1 regioisomeric ratio. ^{1}H NMR was consistent with literature data:[386] IR ($CDCl_3$) 3690, 2941, 2862, 2360, 1709, 1648, 1614, 1448, 1298, 1261, 1218, 1178, 1083 cm^{-1}; mass spectrum (CI) *m/z* 239.1638 [$C_{14}H_{23}O_3$ (M+1) requires 239.1647] 239, 171 (base), 167, 125.

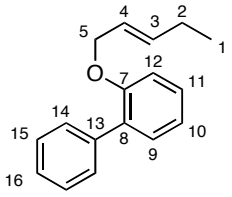


3.97c

1-(1,1-Dimethyl-allyl)-2-oxo-cyclohexanecarboxylic acid ethyl ester (3.97c). (BLA-V-43). -Ketoester **3.97c** was obtained in 74% yield (0.34 mmol scale) in THF after 20 h at room temperature (General Workup B) as a clear, colorless oil after chromatography (hexanes/EtOAc = 5:1) in a 90:10 regioisomeric ratio: ^{1}H NMR (400 MHz) 6.21 (dd, *J* = 17.6, 10.4 Hz, 1 H), 4.98 (dd, *J* = 10.4, 1.2 Hz, 1 H), 4.95 (dd, *J* = 17.6, 1.2 Hz, 2 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 2.52-2.46 (m, 1 H), 2.39-2.77 (m, 1 H), 2.27-2.22 (comp, 2 H), 1.71-1.49 (comp, 4 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.21 (s, 3 H),

1.13 (s, 3 H); ^{13}C NMR (100 MHz) □ 206.6, 171.9, 145.1, 112.2, 65.9, 60.9, 42.8, 32.2, 29.0, 26.6, 22.3, 14.1; IR ($CDCl_3$) 2941, 2868, 2257, 2082, 2009, 1707, 1298, 1260, 1218, 1082, 1016 cm^{-1}; mass spectrum (CI) *m/z* 239.1642 [$C_{14}H_{23}O_3$ (M+1) requires 239.1647] 239 (base), 221, 172.

NMR Assignments: ^{1}H NMR (400 MHz) □ 6.21 (dd, *J* = 17.6, 10.4 Hz, 1 H, C2-H), 4.98 (dd, *J* = 10.4, 1.2 Hz, 1 H, C1-H), 4.95 (dd, *J* = 17.6, 1.2 Hz, 2 H, C1-H), 4.21 (q, *J* = 7.2 Hz, 2 H, C12-H), 2.52-2.46 (m, 1 H, C7-H), 2.39-2.77 (m, 1 H), 2.27-2.22 (comp, 2 H), 1.71-1.49 (comp, 4 H), 1.30 (t, *J* = 7.2 Hz, 3 H, C13-H), 1.21 (s, 3 H, C4-H), 1.13 (s, 3 H, C4-H); ^{13}C NMR (100 MHz) □ 206.7 (C6), 171.9 (C11), 145.1 (C2), 112.2 (C1), 65.9 (C5), 60.9 (C12), 42.8 (C7), 32.2 (C3), 29.0 (C9), 26.6 (C8), 22.9 (C10), 22.3 (C4), 14.1 (C13).



3.99

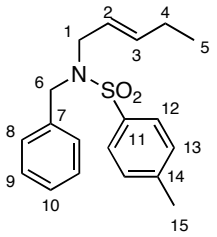
2-Phenyl-1-((*E*)-pent-2-enyloxy) benzene (3.99) (BLA-V-167). A 1.0 M solution of LiHMDS (0.66 mL, 0.66 mmol) was added to a slurry of 2-phenylphenol (**3.98**) (118 mg, 0.69 mmol) and CuI (132 mg, 0.69 mmol) in THF (1.5 mL) at room temperature. The mixture was stirred at rt for 30 min. In a separate flask, $[Rh(CO)_2Cl]_2$ (13 mg, 0.034 mmol) was dissolved in THF (2 mL), stirred for 5 min at rt then transferred *via* syringe to the flask containing phenoxide. Carbonate **3.14a** was then added to the mixture, and the reaction was stirred at rt for 24 h. The mixture was filtered through a

short plug of SiO_2 eluting with Et_2O (50 mL). The eluent was concentrated under reduced pressure, and the crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to provide 67 mg (84%) of **3.99** as a clear, brown oil: ^{1}H NMR (500 MHz) δ 7.57-7.54 (comp, 2 H), 7.41-7.37 (comp, 2 H), 7.34-7.28 (comp, 3 H), 7.06-6.96 (comp, 2 H), 5.78 (dtt, *J* = 15.4, 7.8, 1.4 Hz, 1 H), 5.60 (dtt, *J* = 15.4, 5.6, 1.6 Hz, 1 H), 4.48 (ddt, *J* = 5.6, 2.5, 1.6 Hz, 2 H), 2.08-2.02 (m, 2 H), 0.98 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz) δ 155.7, 138.6, 137.8, 136.1, 130.9, 129.6, 127.9, 126.8, 124.0, 121.0, 113.4, 69.4, 25.3, 13.3; IR ($CHCl_3$) 2964, 1596, 1480, 1434, 1255, 1216, 912, 846 cm^{-1}; mass spectrum (CI) *m/z* 239.1426 [$C_{17}H_{19}O_1$ (M+1) requires 239.1436] 243, 239, 199, 171 (base).

NMR Assignments: ^{1}H NMR (500 MHz) δ 7.57-7.54 (comp, 2 H), 7.41-7.37 (comp, 2 H), 7.34-7.28 (comp, 3 H), 7.06-6.96 (comp, 2 H), 5.78 (dtt, *J* = 15.4, 7.8, 1.4 Hz, 1 H, C3-H), 5.60 (dtt, *J* = 15.4, 5.6, 1.6 Hz, 1 H, C4-H), 4.48 (ddt, *J* = 5.6, 2.5, 1.6 Hz, 2 H, C5-H), 2.08-2.02 (m, 2 H, C2-H), 0.98 (t, *J* = 7.5 Hz, 3 H, C1-H); ^{13}C NMR (125 MHz) δ 155.7, 138.6, 137.8, 136.1 (C3), 130.9, 129.6, 127.9, 126.8, 124.0 (C4), 121.0, 113.4, 69.4 (C5), 25.3 (C2), 13.3 (C1).

General Procedure for the $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Amination of Unsymmetrical Allylic Carbonates with Sulfonamides. $[Rh(CO)_2Cl]_2$ (5 mol %) was dissolved in dry, degassed THF (5 mL), the allylic substrate (1.0 mmol) was added, and the solution stirred for 30 min at room temperature. In a separate flask, a 1.0 M solution of LDA in THF was added to a solution of sulfonamide (0.29 mL, 2.5 mmol) in THF (5 mL) and stirred for 20 min at room temperature. The resulting amide was added *via* syringe to the solution of allylic substrate and $[Rh(CO)_2Cl]_2$ at room temperature. The mixture was then sealed in a screw cap vial under argon and stirred for 2 h at room

temperature. The resulting dark brown solution was then filtered through a short plug of silica gel eluting with Et_2O (50 mL), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O to provide the amination products in the specified ratios.

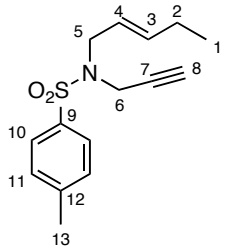


3.109b

(*E*)-*N*-benzyl-4-methyl-*N*-(pent-2-enyl)benzenamine (3.109b) (BLA-VI-171). The reaction was performed on a 0.34 mmol scale, and LiHMDS was used in place of LDA. After stirring at room temperature for 24 h, flash chromatographic purification eluting with pentane/Et_2O (5:1) as described above (General Procedure), provided 79 mg (71%) of **3.109b** in a ratio of 82:18 ratio of regioisomers as a clear colorless oil: ^{1}H NMR (500 MHz) δ 7.73 (d, J = 6.8 Hz, 2 H), 7.57-7.54 (comp, 7 H), 5.42 (dddt, J = 12.4, 6.4, 5.6, 1.6 Hz, 1 H), 5.06 (dddt, J = 12.4, 6.8, 5.6, 1.2 Hz, 1 H), 4.32 (s, 2 H), 3.69 (br d, J = 5.6 Hz, 2 H), 2.44 (s, 3 H), 1.91-1.86 (m, 2 H), 0.84 (t, J = 6.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 143.1, 137.7, 137.6, 136.3, 129.6, 128.4, 128.4, 127.2, 122.0, 50.0, 48.9, 25.1, 21.5, 13.1; mass spectrum (CI) m/z 330.1531 [$C_{19}H_{24}NO_2S$ (M+1) requires 330.1528] 330 (base), 274.

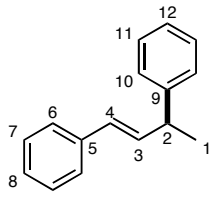
NMR Assignments: ^{1}H NMR (500 MHz) δ 7.73 (d, J = 6.8 Hz, 2 H, C_{AR}-H), 7.57-7.54 (comp, 7 H, C_{AR}-H), 5.42 (dddt, J = 12.4, 6.4, 5.6, 1.6 Hz, 1 H, C4-H), 5.06 (dddt, J = 12.4, 6.8, 5.6, 1.2 Hz, 1 H, C3-H), 4.32 (s, 2 H, C6-H), 3.69 (br d, J = 5.6 Hz, 2

H, C5-H), 2.44 (s, 3 H, C15-H), 1.91-1.86 (m, 2 H, C2-H), 0.84 (t, J = 6.0 Hz, 3 H, C1-H); ^{13}C NMR (125 MHz) 143.1 (C14), 137.7 (C4), 137.6, 136.3, 129.6, 128.4, 128.4, 127.2, 122.0 (C3), 50.0 (C6), 48.9 (C5), 25.1 (C2), 21.5 (C15), 13.1 (C1).



3.109c

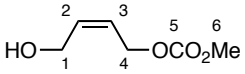
(*E*)-4-methyl-*N*-(pent-2-enyl)-*N*-(prop-2-ynyl)benzenamine (3.109c) (BLA-IV-275). The reaction was performed on a 0.14 mmol scale, and LiHMDS was used in place of LDA. After stirring at room temperature for 2 h, flash chromatographic purification eluting with pentane/Et_2O (5:1) as described above (General Procedure), provided 16 mg (42%) of **3.109c** as a clear colorless oil. ^{1}H NMR and ^{13}C NMR were consistent with literature data.[387]



3.122

(*S*,*E*)-1,3-diphenylbut-1-ene (3.122) (BLA-VIII-111). A 2.35 M solution of *n*-BuLi (0.22 mL, 0.51 mmol) in hexanes was added to a solution bromobenzene (80 mg,

0.05 mL, 0.51 mmol) in THF (1.5 mL) at –78 ˚C and stirred for 1 h. The mixture was allowed to warm to 0 ˚C by exchange of cooling baths and a solution of $ZnBr_2$ (109 mg, 0.48 mmol) in THF (0.5 mL) was added. The resulting mixture was stirred for 30 min then added to a solution of **(+)-3.47** in THF (1 mL) at 0 ˚C and the reaction stirred for 15 min. The reaction was diluted with saturated sodium $NaHCO_3$ (3 mL), allowed to warm to room temperature and the layers separated. The aqueous phase was extracted with Et_2O (3 x 3 mL), the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to give 48 mg (99%) as a clear, colorless oil whose spectral properties and optical rotation were consistent with literature data.[388]

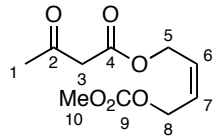


3.123

(*Z*)-4-Hydroxybut-2-enyl methyl carbonate (3.123) (BLA-VI-153). Methyl chloroformate (0.88 mL, 11.3 mmol) was added to a solution of *cis*-2-butene-1,4-diol (**3.23**) (0.94 mL, 11.3 mmol) and pyridine (0.92 mL, 11.3 mmol) in CH_2Cl_2 (25 mL) at 0 ˚C and stirred for 30 min. The reaction was allowed to warm to room temperature by removal of the cooling bath and stirred for 2 h. Saturated aqueous NaCl (25 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 25 mL) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (1:1) to provide 946 mg (57%) of **3.123** as a clear, colorless oil: ^{1}H NMR (400 MHz) □ 5.91 (dtt, *J* = 11.2, 6.8, 0.8

Hz, 1 H), 5.68 (dtt, *J* = 11.2, 7.2, 1.2 Hz, 1 H), 4.74 (dd, *J* = 6.8, 1.2 Hz, 2 H), 4.27 (app t, *J* = 6.0 Hz, 2 H), 3.79 (s, 3 H), 2.01 (br t, *J* = 6.0 Hz, 1 H); ^{13}C NMR (100 MHz) 155.6, 133.9, 124.4, 63.1, 57.9, 54.7; IR ($CHCl_3$) 3610, 3502, 3024, 2959, 1746, 1444, 1277, 1019, 942, 908 cm^{-1}; mass spectrum (CI) *m/z* 147.0654 [$C_6H_{11}O_4$ (M+1) requires 147.0657] 147 (base), 129.

NMR Assignments: ^{1}H NMR (400 MHz) 5.91 (dtt, *J* = 11.2, 6.8, 0.8 Hz, 1 H, C2-H), 5.68 (dtt, *J* = 11.2, 7.2, 1.2 Hz, 1 H, C3-H), 4.74 (dd, *J* = 6.8, 1.2 Hz, 2 H, C1-H), 4.27 (app t, *J* = 6.0 Hz, 2 H, C4-H), 3.79 (s, 3 H, C5-H), 2.01 (br t, *J* = 6.0 Hz, 1 H, O-H); ^{13}C NMR (100 MHz) 155.6 (C5), 133.9 (C3), 124.4 (C2), 63.1 (C4), 57.9 (C1), 54.7 (C6).

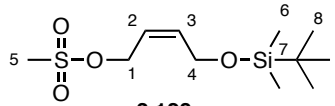


3.124

(*Z*)-4-(3-oxobutanoxy)-but-2-enyl methyl carbonate (3.124) (BLA-VI-157). Diketene (0.53 mL, 6.8 mmol) was added dropwise to a solution of alcohol **3.123** (500 mg, 3.42 mmol) and DMAP (56 mg, 0.68 mmol) in THF (17 mL) with stirring at 0 °C. The reaction was allowed to warm to room temperature by removal of the cooling bath and stirred for 1 h. Saturated aqueous NH_4Cl (20 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined organic fractions were washed with saturated aqueous NaCl (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (1:1) to provide 574 mg (73%) of **3.124** as a

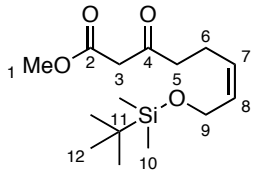
clear, colorless oil: ^{1}H NMR (400 MHz) δ 5.85-5.75 (comp, 2 H), 4.76 (d, *J* = 8.0 Hz, 2 H), 4.75 (d, *J* = 8.0 Hz, 2 H), 3.79 (s, 3 H), 3.48 (s, 2 H), 2.27 (s, 3 H); ^{13}C NMR (100 MHz) δ 200.2, 166.7, 155.4, 127.9, 127.8, 63.0, 60.5, 54.7, 49.7, 30.0; IR ($CHCl_3$) 3024, 1748, 1720, 1650, 144, 1348, 1273, 1151, 966 cm^{-1}; mass spectrum (CI) *m/z* 231.0874 [$C_{10}H_{15}O_6$ (M+1) requires 231.0869] 231, 155 (base), 129.

NMR Assignments: ^{1}H NMR (400 MHz) δ 5.85-5.75 (comp, 2 H, C6-C7-H), 4.76 (d, *J* = 8.0 Hz, 2 H, C5-H), 4.75 (d, *J* = 8.0 Hz, 2 H, C8-H), 3.79 (s, 3 H, C10-H), 3.48 (s, 2 H, C3-H), 2.27 (s, 3 H, C1-H); ^{13}C NMR (100 MHz) δ 200.2 (C2), 166.7 (C4), 155.4 (C9), 127.9 (C7), 127.8 (C6), 63.0 (C8), 60.5 (C5), 54.7 (C10), 49.7 (C3), 30.0 (C1).



3.128

(*Z*)-4-(*tert*-butyldimethylsilyloxy)but-2-enyl methanesulfonate (3.128) (BLA-VI-188). Methanesulfonyl chloride (0.17 mL, 1.97 mmol) was added to a solution of **3.127** (400 mg, 1.97 mmol) and Et_3N (0.40 mL, 2.96 mmol) in CH_2Cl_2 (10 mL) and stirred for 1 h at 0 ˚C. Saturated aqueous $NaHCO_3$ (10 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The ^{1}H NMR of the crude residue was consistent with literature data for **3.128** and was therefore used without further purification.[389]

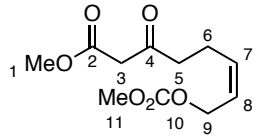


3.129

(*Z*)-methyl 8-(*tert*-butyldimethylsilyloxy)-3-oxooct-6-enoate (3.129) (BLA-VI-210). Methyl acetoacetate (0.86 mL, 7.99 mmol) was added to a slurry of NaH (320 mg of a 60% mineral oil suspension, 7.99 mmol) in THF (20 mL) and stirred for 20 min at room temperature. A 1.0 M solution in THF of LDA (0.49 mL, 0.49 mmol) was added at room temperature and the reaction stirred for 30 min. The mixture was cooled to 0 °C and a solution of **3.128** (1.49 g, 5.30 mmol) in THF (7 mL) was added dropwise *via* syringe and stirred for 4 h. Saturated aqueous $NaHCO_3$ (25 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 25 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to provide 878 mg (55%) of **3.129** as a clear, colorless oil: ^{1}H NMR (400 MHz) □ 5.56 (dtt, *J* = 10.8, 6.4, 1.2 Hz, 1 H), 5.37 (dtt, *J* = 10.8, 7.6, 1.2 Hz, 1 H), 4.23 (m, 2 H), 3.74 (s, 3 H), 3.45 (s, 2 H), 2.62 (t, *J* = 7.2 Hz, 2 H), 2.34 (m, 2 H), 0.90 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz) □ 201.7, 167.4, 131.0, 128.2, 59.2, 52.2, 48.9, 42.5, 25.8, 25.6, 18.2, -5.3; IR ($CHCl_3$) 2955, 2929, 2856, 1742, 1716, 1471, 1361, 1254, 1072, 1005, 838 cm^{-1}; mass spectrum (CI) *m/z* 301.1823 [$C_{15}H_{29}O_4Si$ (M+1) requires 301.1835] 301, 243, 169 (base).

NMR Assignments: ^{1}H NMR (400 MHz) □ 5.56 (dtt, *J* = 10.8, 6.4, 1.2 Hz, 1 H, C8-H), 5.37 (dtt, *J* = 10.8, 7.6, 1.2 Hz, 1 H, C7-H), 4.23 (m, 2 H, C9-H), 3.74 (s, 3 H, C1-H), 3.45 (s, 2 H, C3-H), 2.62 (t, *J* = 7.2 Hz, 2 H, C5-H), 2.34 (m, 2 H, C6-H), 0.90 (s, 9

H, C12-H), 0.07 (s, 6 H, C10-H); ^{13}C NMR (100 MHz) 201.7 (C4), 167.4 (C2), 131.0 (C8), 128.2 (C7), 59.2 (C9), 52.2 (C1), 48.9 (C3), 42.5 (C5), 25.8 (C12), 25.6 (C6), 18.2 (C11), -5.3 (C10).

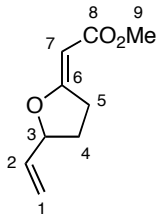


3.130

(*Z*)-Methyl 8-(methoxycarbonyloxy)-3-oxooct-6-enoate (3.130) (BLA-VI-200). A solution of TBAF (154 mg, 0.59 mmol) in THF (0.59 mL) was added to a solution of **3.129** in THF (2 mL) and stirred for 3 h at room temperature. Saturated aqueous NaCl (2 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 2 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (1 mL) and cooled to 0 ˚C. Pyridine (0.05mL, 0.58 mmol) and methyl chloroformate (0.05 mL, 0.56 mmol) were added sequentially and the reaction allowed to warm to room temperature by removal of the cooling bath and stirred for 30 min. Saturated aqueous NaCl (1 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 1 mL), and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to provide 27 mg (57%) of **3.130** as a clear, colorless oil: ^{1}H NMR (400 MHz) 5.66-5.56 (m, 2 H), 4.71 (d, J = 5.6 Hz, 2 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.47 (s, 2 H), 2.66 (t, J = 7.2 Hz, 2 H), 2.42 (app t, J = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz) 201.3, 167.3, 155.5,

149.6, 133.2, 63.2, 54.5, 52.1, 48.8, 42.0, 21.3; IR ($CHCl_3$) 3025, 2957, 1747, 1443, 1271, 948 cm^{-1}; mass spectrum (CI) *m/z* 245.1029 [$C_{11}H_{17}O_6$ (M+1) requires 245.1025] 245 (base), 169.

NMR Assignments: ^{1}H NMR (400 MHz) □ 5.66-5.56 (m, 2 H, C7-C8-H), 4.71 (d, *J* = 5.6 Hz, 2 H, C9-H), 3.78 (s, 3 H, C11-H), 3.74 (s, 3 H, C1-H), 3.47 (s, 2 H, C3-H), 2.66 (t, *J* = 7.2 Hz, 2 H, C5-H), 2.42 (app t, *J* = 7.2 Hz, 2 H, C6-H); ^{13}C NMR (100 MHz) □ 201.3 (C4), 167.3 (C2), 155.5 (C10), 149.6 (C8), 133.2 (C7), 63.2 (C9), 54.5 (C11), 52.1 (C1), 48.8 (C3), 42.0 (C5), 21.3 (C6).

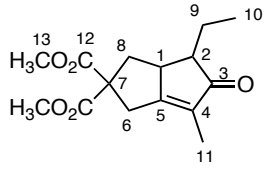


3.131

(*E*)-methyl 2-(5-vinyl-dihydrofuran-2(3*H*)-ylidene)acetate (3.131) (BLA-VI-216). **3.130** (50 mg, 0.20 mmol) was added to a slurry of NaH (5 mg of a 60% mineral oil suspension, 0.20 mmol) in DMF (2 mL) and stirred for 30 min at room temperature. $[Rh(CO)_2Cl]_2$ (8 mg, 0.02 mmol) was added and the reaction stirred for 2 h. Saturated aqueous NH_3Cl (2 mL) and Et_2O (2 mL) were added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 2 mL) and the combined organic fractions were washed with saturated aqueous NaCl (2 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to provide 24 mg (71%) of **3.131** as a clear, colorless oil: ^{1}H NMR (500 MHz) □ 5.86 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1 H), 5.34 (app t, *J* = 2.0 Hz, 1 H),

5.33 (app dt, *J* = 17.0, 1.5 Hz, 1 H), 5.23 (app dt, *J* = 10.5, 1.5 Hz, 1 H), 4.85-4.80 (m, 1 H), 3.66 (s, 3 H), 3.27 (dddd, *J* = 18.5, 9.0, 5.0, 2.0 Hz, 1 H), 3.02 (dddd, *J* = 18.5, 9.0, 8.5, 2.0 Hz, 1 H), 2.30-2.23 (m, 1 H), 1.85 (dddd, *J* = 16.5, 8.5, 7.5, 5.0 Hz, 1 H); ^{13}C NMR (125 MHz) □ 176.2, 169.0, 135.9, 117.6, 89.4, 83.9, 50.7, 30.2, 29.8; mass spectrum (CI) *m/z* 169.0870 [$C_9H_{13}O_3$ (M+1) requires 169.0865] 169 (base), 137.

NMR Assignments: ^{1}H NMR (500 MHz) □ 5.86 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1 H, C2-H), 5.34 (app t, *J* = 2.0 Hz, 1 H, C7-H), 5.33 (app dt, *J* = 17.0, 1.5 Hz, 1 H, C1-H), 5.23 (app dt, *J* = 10.5, 1.5 Hz, 1 H, C1-H), 4.85-4.80 (m, 1 H, C3-H), 3.66 (s, 3 H, C9-H), 3.27 (dddd, *J* = 18.5, 9.0, 5.0, 2.0 Hz, 1 H, C5-H), 3.02 (dddd, *J* = 18.5, 9.0, 8.5, 2.0 Hz, 1 H, C5-H), 2.30-2.23 (m, 1 H, C4-H), 1.85 (dddd, *J* = 16.5, 8.5, 7.5, 5.0 Hz, 1 H, C4-H); ^{13}C NMR (125 MHz) □ 176.2 (C6), 169.0 (C8), 135.9 (C2), 117.6 (C1), 89.4 (C7), 83.9 (C3), 50.7 (C9), 30.2 (C5), 29.8 (C4).

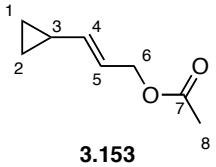


3.143

4-Ethyl-6-methyl-5-oxo-3,3a,4,5-tetrahydro-1*H*-pentalene-2,2-dicarboxylic acid dimethyl ester (3.143). **(BLA-IV-204)**. A solution of **3.89c** (10 mg, 40.0 □mol) in Bu_2O (0.4 mL) was added to a flask charged with $[Rh(CO)_2Cl]_2$ (2 mg, 3.9 □mol) under an atmosphere of CO (balloon) and heated under reflux for 24 h. The solution was allowed to cool to room temperature, filtered through a short plug of neutral alumina eluting with EtOAc (25 mL), and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give

11 mg (99%) of **3.143** as a clear, colorless oil: ^{1}H NMR (500 MHz) δ 3.80 (s, 3 H), 3.76 (s, 3 H), 3.23 (d, *J* = 18.8 Hz, 1 H), 3.17 (d, *J* = 18.8 Hz, 1 H), 2.82 (dd, *J* = 12.7, 7.5 Hz, 1 H), 2.69-2.65 (m, 1 H), 2.00 (app dt, *J* = 9.7, 3.9 Hz, 1 H), 1.94 (ddq, *J* = 14.0, 7.5, 4.1 Hz, 1 H), 1.76-1.70 (m, 1 H), 1.71 (app dt, *J* = 3.4, 2.4 Hz, 3 H), 1.41 (ddq, *J* = 14.0, 9.7, 7.2 Hz, 1 H), 0.98 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz) δ 210.6, 175.2, 172.2, 171.5, 132.5, 61.3, 55.8, 53.2, 53.1, 49.3, 39.5, 34.0, 22.2, 12.1, 8.7; IR ($CDCl_3$) 3691, 2957, 2874, 2358, 2257, 1791, 1705, 1671, 1601, 1436, 1276, 1075 cm^{-1}; mass spectrum (CI) *m*/*z* 281 (base).

NMR Assignments: ^{1}H NMR (400 MHz) δ 3.80 (s, 3 H, C13-H), 3.76 (s, 3 H, C13-H), 3.23 (d, *J* = 18.8 Hz, 1 H, C6-H), 3.17 (d, *J* = 18.8 Hz, 1 H, C6-H), 2.82 (dd, *J* = 12.7, 7.5 Hz, 1 H, C8-H), 2.69-2.65 (m, 1 H, C8-H), 2.00 (app dt, *J* = 9.7, 3.9 Hz, 1 H, C2-H), 1.94 (ddq, *J* = 14.0, 7.5, 4.1 Hz, 1 H, C9-H), 1.76-1.70 (m, 1 H, C1-H), 1.71 (app dt, *J* = 3.4, 2.4 Hz, 3 H, C11-H), 1.41 (ddq, *J* = 14.0, 9.7, 7.2 Hz, 1 H, C9-H), 0.98 (t, *J* = 7.5 Hz, 3 H, C10-H); ^{13}C NMR (125 MHz) δ 210.6 (C4), 175.2 (C2), 172.2 (C12), 171.5 (C12), 132.5 (C3), 61.3 (C7), 55.8 (C5), 53.2 (C13), 53.1 (C13), 49.3 (C1), 39.5 (C8), 34.0 (C6), 22.2 (C9), 12.1 (C10), 8.7 (C11).

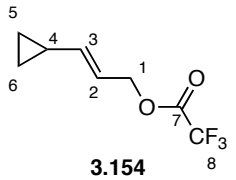


3.153

Acetic acid 3-cyclopropylallyl ester (3.153). (BLA-V-150). Acetyl chloride (1.10 g, 0.51 mL, 7.14 mmol) was added to a solution of **3.22** (350 mg, 3.57 mmol) and pyridine (978 mg, 0.58 mL, 7.14 mmol) in CH_2Cl_2 (16 mL) at 0 °C. The reaction was

allowed to warm to room temperature by removal of the cooling bath and stirred for 3 h. Saturated aqueous $NaHCO_3$ (10 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to give **3.153** as a clear, colorless oil: ^{1}H NMR (400 MHz) δ 5.65 (dt, *J* = 15.2, 6.8 Hz, 1 H), 5.29 (br dd, *J* = 15.2, 8.9 Hz, 1 H), 4.89 (dd, *J* = 6.8, 1.0 Hz, 2 H), 2.06 (s, 3 H), 1.46-1.37 (m, 1 H), 0.74 (dddd, *J* = 10.6, 6.5, 4.4, 4.4 Hz, 2 H), 0.43-0.39 (m, 2 H); ^{13}C NMR (100 MHz) δ 170.9, 140.7, 121.1, 65.2, 21.0, 13.5, 6.8; IR ($CDCl_3$) 3009, 2255, 1732, 1371, 1236, 1025, 956 cm^{-1}; mass spectrum (CI) *m/z* 139.0760 [$C_8H_{11}O_2$ (M-1) requires 139.0759] 139 (base).

NMR Assignments: ^{1}H NMR (400 MHz) δ 5.65 (dt, *J* = 15.2, 6.8 Hz, 1 H, C5-H), 5.29 (br dd, *J* = 15.2, 8.9 Hz, 1 H, C4-H), 4.89 (dd, *J* = 6.8, 1.0 Hz, 2 H, C6-H), 2.06 (s, 3 H, C8-H), 1.46-1.37 (m, 1 H, C3-H), 0.74 (dddd, *J* = 10.6, 6.5, 4.4, 4.4 Hz, 2 H, C2-H), 0.43-0.39 (m, 2 H, C1-H); ^{13}C NMR (100 MHz) δ 170.9 (C7), 140.7 (C4), 121.1 (C5), 65.2 (C6), 21.0 (C8), 13.5 (C3), 6.8 (C1,C2).

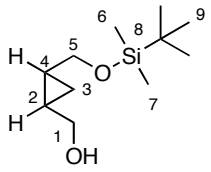


3.154

(*E*)-3-cyclopropylallyl 2,2,2-trifluoroacetate (3.154). **(BLA-VIII-37)**. Trifluoroacetic anhydride (129 mg, 0.61 mmol, 0.09 mL) was added to a solution of **3.158a** (50 mg, 0.51 mmol) in Et_2O (3 mL) at 0 °C. The reaction was allowed to warm to room temperature by removal of the cooling bath and stirred for 15 min. Saturated

aqueous $NaHCO_3$ (3 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 3 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to provide 66 mg (65%) of **3.161** as a clear colorless oil: ^{1}H NMR (400 MHz) 5.68 (dt, *J* = 15.2, 7.2 Hz, 1 H), 5.41 (dd, *J* = 15.2, 9.2 Hz, 1 H), 4.75 (d, *J* = 7.2 Hz, 2 H), 1.49-1.40 (m, 1 H), 0.79 (ddt, *J* = 12.4, 6.4, 4.4 Hz, 2 H), 0.45 (ddt, *J* = 11.2, 6.4, 4.8 Hz, 2 H); ^{13}C NMR (100 MHz) 157.1, 144.1, 118.6, 115.9, 68.7, 13.5, 7.0; IR ($CDCl_3$) 3689, 3009, 1780, 1667, 1602, 1337, 1223, 1173, 1149 cm^{-1}; mass spectrum (CI) *m/z* 194.0560 [$C_8H_9O_2F_3$ (M+1) requires 194.0555] 195, 183 (base), 179.

NMR Assignments: ^{1}H NMR (400 MHz) 5.68 (dt, *J* = 15.2, 7.2 Hz, 1 H, C2-H), 5.41 (dd, *J* = 15.2, 9.2 Hz, 1 H, C3-H), 4.75 (d, *J* = 7.2 Hz, 2 H, C1-H), 1.49-1.40 (m, 1 H, C4-H), 0.79 (ddt, *J* = 12.4, 6.4, 4.4 Hz, 2 H, C5-C6-H), 0.45 (ddt, *J* = 11.2, 6.4, 4.8 Hz, 2 H, C5,6-H); ^{13}C NMR (100 MHz) 157.1 (C7), 144.1 (C3), 118.6 (C2), 115.9 (C8), 68.7 (C1), 13.5 (C4), 7.0 (C5,6).

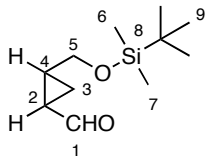


3.155

(2-((*tert*-butyldimethylsilyloxy)methyl)cyclopropyl)methanol (3.155). (BLA-VII-49). Diiodomethane (2.91 g, 0.88 mL, 10.9 mmol) was added to a solution of Et_2Zn (1.0 M in hexane, 5.9 mmol, 5.9 mL) in CH_2Cl_2 (20 mL) at 0 ˚C and stirred for 15 min. The resulting white slurry was cooled to –78 ˚C and a solution of **3.154** (500 mg, 2.47 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction was allowed to warm slowly

to 0 ˚C by exchange of cooling baths and stirred for 1 h. The mixture was then allowed to warm to room temperature by removal of the cooling bath and stirred for an additional 2 h. The reaction was cooled to 0 ˚C, saturated aqueous NH_4Cl (12 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 12 mL) and the combined organic fractions dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to give 421 mg (79%) of **3.155** as a clear, colorless oil: ^{1}H NMR (400 MHz) δ 4.15 (dd, *J* = 11.6, 5.6 Hz, 1 H), 3.97 (ddd, *J* = 17.6, 12.4, 5.6 Hz, 1 H), 3.29-3.21 (comp, 3 H), 1.42-1.32 (m, 1 H), 1.23 (dddt, *J* = 13.6, 11.2, 5.6, 5.2 Hz, 1 H), 0.92 (s, 9 H), 0.76 (ddd, *J* = 13.6, 8.4, 5.2 Hz, 1 H), 0.91 (dq, *J* = 10.0, 5.2 Hz, 1 H), 0.12 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (100 MHz) δ 63.7, 62.9, 25.7, 18.1, 18.0, 17.2, 8.2, -5.4, -5.7; IR ($CDCl_3$) 3454, 2956, 2930, 2858, 16012, 1471, 1257, 1216, 1057, 1036 cm^{-1}; mass spectrum (CI) *m/z* 217.1615 [$C_{11}H_{25}O_2Si$ (M+1) requires 217.1624] 217, 199 (base), 133.

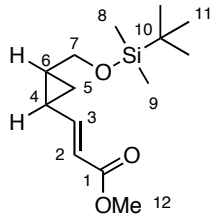
NMR Assignments: ^{1}H NMR (400 MHz) δ 4.15 (dd, *J* = 11.6, 5.6 Hz, 1 H, C5-H), 3.97 (ddd, *J* = 17.6, 12.4, 5.6 Hz, 1 H, C1-H), 3.29-3.21 (comp, 3 H, C1-C5-O-H), 1.42-1.32 (m, 1 H, C2-H), 1.23 (dddt, *J* = 13.6, 11.2, 5.6, 5.2 Hz, 1 H, C4-H), 0.92 (s, 9 H, C9-H), 0.76 (ddd, *J* = 13.6, 8.4, 5.2 Hz, 1 H, C3-H), 0.91 (dq, *J* = 10.0, 5.2 Hz, 1 H, C3-H), 0.12 (s, 3 H, C6-H), 0.10 (s, 3 H, C7-H); ^{13}C NMR (100 MHz) δ 63.7 (C5), 62.9 (C1), 25.7 (C9), 18.1 (C4), 18.0 (C8), 17.2 (C2), 8.2 (C3), -5.4 (C6), -5.7 (C7).



3.156

2-((*tert*-butyldimethylsilyloxy)methyl)cyclopropanecarbaldehyde (3.156). (BLA-VII-218). 4 Å MS (630 mg) and NMO (256 mg, 2.1 mmol) were added sequentially to a solution of **3.155** in CH_2Cl_2 (7 mL) at room temperature and stirred for 10 min. TPAP (26 mg, 0.07 mmol) was then added and stirring continued for 6 h at room temperature. The crude mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (2:1) to give 272 mg (88%) of **3.156a** as a clear, colorless oil: ^{1}H NMR (400 MHz) 9.43 (d, *J* = 5.2 Hz, 1 H), 3.98 (dd, *J* = 11.2, 5.2 Hz, 1 H), 3.63 (dd, *J* = 11.2, 7.6 Hz, 1 H), 1.97 (m, 1 H), 1.82-1.73 (m, 1 H), 1.34 (ddd, *J* = 10.0, 6.8, 5.2 Hz, 1 H), 1.28-1.20 (m, 1 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (100 MHz) 200.8, 62.8, 27.4, 26.2, 25.8, 18.2, 12.0, -5.4, -5.4; IR ($CDCl_3$) 3691, 2956, 2938, 2858, 2254, 1699, 1601, 1256, 1089 cm^{-1}; mass spectrum (CI) *m/z* 215.1460 [$C_{11}H_{23}O_2Si$ (M+1) requires 215.1467] 215 (base), 157.

NMR Assignments: ^{1}H NMR (400 MHz) 9.43 (d, *J* = 5.2 Hz, 1 H, C1-H), 3.98 (dd, *J* = 11.2, 5.2 Hz, 1 H, C4-H), 3.63 (dd, *J* = 11.2, 7.6 Hz, 1 H, C4-H), 1.97 (m, 1 H, C2-H), 1.82-1.73 (m, 1 H, C3-H), 1.34 (ddd, *J* = 10.0, 6.8, 5.2 Hz, 1 H, C5-H), 1.28-1.20 (m, 1 H, C5-H), 0.88 (s, 9 H, C9-C10-C11-H), 0.05 (s, 3 H, C6-H), 0.05 (s, 3 H, C7-H); ^{13}C NMR (100 MHz) 200.8 (C1), 62.8 (C5), 27.4 (C2), 26.2 (C4), 25.8 (C9), 18.2 (C8), 12.0 (C3), -5.4 (C6), -5.4 (C7).

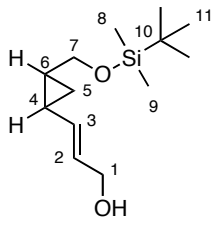


3.157

(*E*)-methyl 3-(2-((*tert*-butyldimethylsilyloxy)methyl)cyclopropyl)acrylate (3.157). (BLA-VII-36). Trimethyl phosphonoacetate (639 mg, 3.5 mmol, 0.57 mL) was added to a slurry of NaH (133 mg of a 60% mineral oil suspension, 3.33 mmol) in THF (5 mL) at 0 ˚C and stirred for 1 h. A solution of **3.156** (376 mg, 1.75 mmol) in THF (4 mL) was added, the mixture allowed to warm to room temperature by removal of the cooling bath and stirred for 2 h. H_2O (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give 468 mg (99%) of **3.157** as a clear, colorless oil: ^{1}H NMR (400 MHz) □ 6.74 (dd, *J* = 15.2, 10.0 Hz, 1 H), 5.93 (d, *J* = 15.2 Hz, 1 H), 3.82 (dd, *J* = 11.2, 6.0 Hz, 1 H), 3.71 (s, 3 H), 3.61 (dd, *J* = 11.2, 7.2 Hz, 1 H), 1.71-1.68 (m, 1 H), 1.55-1.48 (m, 1 H), 1.14 (ddd, *J* = 13.2, 8.4, 4.8 Hz, 1 H), 0.89 (s, 9 H), 0.72 (dd, *J* = 11.6, 5.2 Hz, 1 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (100 MHz) □ 166.8, 150.3, 119.8, 62.5, 51.2, 25.8, 23.3, 19.3, 18.3, 12.9, -5.4, -5.4; IR ($CDCl_3$) 2954, 2929, 2857, 1711, 1646, 1437, 1270, 1148, 1074 cm^{-1}; mass spectrum (CI) *m/z* 271.1742 [$C_{14}H_{27}O_3Si$ (M+1) requires 271.1730] 271, 255, 213, 139 (base).

NMR Assignments: ^{1}H NMR (400 MHz) □ 6.74 (dd, *J* = 15.2, 10.0 Hz, 1 H, C3-H), 5.93 (d, *J* = 15.2 Hz, 1 H, C2-H), 3.82 (dd, *J* = 11.2, 6.0 Hz, 1 H, C7-H), 3.71 (s, 3 H,

C12-H), 3.61 (dd, *J* = 11.2, 7.2 Hz, 1 H, C7-H), 1.71-1.68 (m, 1 H, C4-H), 1.55-1.48 (m, 1 H, C6-H), 1.14 (ddd, *J* = 13.2, 8.4, 4.8 Hz, 1 H, C5-H), 0.89 (s, 9 H, C11-H), 0.72 (dd, *J* = 11.6, 5.2 Hz, 1 H, C5-H), 0.06 (s, 3 H, C8-H), 0.05 (s, 3 H, C9-H); ^{13}C NMR (100 MHz) 166.8 (C1), 150.3 (C3), 119.8 (C2), 62.5 (C7), 51.2 (C12), 25.8 (C11), 23.3 (C4), 19.3 (C10), 18.3 (C6), 12.9 (C5), -5.4 (C8), -5.4 (C9).

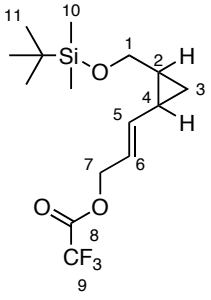


3.158

(*E*)-3-(2-((*tert*-butyldimethylsilyloxy)methyl)cyclopropyl)prop-2-en-1-ol (3.158). (BLA-VII-40). A 1.0M solution of DIBALH in PhMe (5.2 mmol, 5.2 mL) was added to a solution of **3.157** in THF (9 mL) at –78 ˚C. The reaction was allowed to warm to room temperature by removal of the cooling bath and stirred for 2 h at room temperature. The mixture was then cooled to 0 ˚C, saturated Rochelle's salt (10 mL) was added and stirring continued for 30 min. The layers were separated and the aqueous phase extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (2:1) to yield 349 mg (89%) of **3.158** as a clear, colorless oil: ^{1}H NMR (400 MHz) 5.77 (app dt, *J* = 15.2, 5.6 Hz, 1 H), 5.51 (app ddt, *J* = 15.2, 8.4, 0.8 Hz, 1 H), 4.10 (br d, *J* = 5.6 Hz, 1 H), 3.70 (dd, *J* = 11.2, 6.4 Hz, 1 H), 3.56 (dd, *J* = 11.2, 7.2 Hz, 1 H), 1.59 (app ddt, *J* = 14.0, 8.4, 6.4 Hz, 1 H), 1.33-1.24 (m, 1 H), 0.89 (s, 9 H), 0.42 (app q, *J* = 5.6 Hz, 1 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ^{13}C

NMR (100 MHz) δ 131.9, 129.3, 63.5, 63.1, 25.9, 20.6, 18.3, 18.3, 10.6, -5.2, -5.2; IR ($CDCl_3$) 2929, 2857, 2360, 1471, 1255, 1083, 968 cm^{-1}; mass spectrum (CI) *m/z* 243.1785 [$C_{13}H_{27}O_2Si$ (M+1) requires 243.1780] 243 (base), 241.

NMR Assignments: ^{1}H NMR (400 MHz) δ 5.77 (app dt, *J* = 15.2, 5.6 Hz, 1 H, C2-H), 5.51 (app ddt, *J* = 15.2, 8.4, 0.8 Hz, 1 H, C3-H), 4.10 (br d, *J* = 5.6 Hz, 1 H, O-H), 3.70 (dd, *J* = 11.2, 6.4 Hz, 1 H, C7-H), 3.56 (dd, *J* = 11.2, 7.2 Hz, 1 H, C7-H), 1.59 (app ddt, *J* = 14.0, 8.4, 6.4 Hz, 1 H, C6-H), 1.33-1.24 (m, 1 H, C4-H), 0.89 (s, 9 H, C11-H), 0.42 (app q, *J* = 5.6 Hz, 1 H, C5-H), 0.06 (s, 3 H, C8-H), 0.05 (s, 3 H, C9-H); ^{13}C NMR (100 MHz) δ 131.9 (C3), 129.3 (C2), 63.5 (C7), 63.1 (C1), 25.9 (C11), 20.6 (C4), 18.3 (C6), 18.3 (C10), 10.6 (C5), -5.2 (C8), -5.2 (C9).

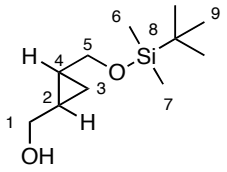


3.159

(*E*)-3-(2-((tert-butyldimethylsilyloxy)methyl)cyclopropyl)allyl 2,2,2-trifluoroacetate (3.159) (BLA-VII-304). Trifluoroacetic anhydride (101 mg, 0.48 mmol, 0.07 mL) was added to a solution of **3.158** (100 mg, 0.44 mmol) in Et_2O (2 mL) at 0 ˚C. The reaction was allowed to warm to room temperature by removal of the ice bath and stirred for 15 min. Saturated aqueous $NaHCO_3$ (3 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 3 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to

provide 143 mg (96%) of **3.159** as a clear colorless oil: ^{1}H NMR (400 MHz) δ 5.71-5.68 (comp, 2 H), 4.75-4.73 (comp, 2 H), 3.74 (dd, *J* = 11.2, 6.0 Hz, 1 H), 3.50 (dd, *J* = 11.2, 7.6 Hz, 1 H), 1.63-1.56 (m, 1 H), 1.38-1.29 (m, 1 H), 0.95 (ddd, *J* = 13.2, 8.4, 5.2 Hz, 1 H), 0.86 (s, 6 H), 0.47 (dd, *J* = 10.8, 5.2 Hz, 1 H), 0.03 (s, 9 H); ^{13}C NMR (100 MHz) δ 157.5, 139.3, 121.1, 115.9, 68.7, 62.8, 25.9, 21.2, 18.5, 18.3, 11.0, -5.3, -5.3; IR ($CDCl_3$) 2929, 2857, 1781, 1472, 1338, 1223, 1174, 1149, 1074 cm^{-1}; mass spectrum (CI) *m/z* 339.1607 [$C_{15}H_{26}O_3F_3Si$ (M+1) requires 339.1603] 338 (base), 306.

NMR Assignments: ^{1}H NMR (400 MHz) δ 5.71-5.68 (comp, 2 H, C5-C6-H), 4.75-4.73 (comp, 2 H, C7-H), 3.74 (dd, *J* = 11.2, 6.0 Hz, 1 H, C1-H), 3.50 (dd, *J* = 11.2, 7.6 Hz, 1 H, C1-H), 1.63-1.56 (m, 1 H, C4-H), 1.38-1.29 (m, 1 H, C2-H), 0.95 (ddd, *J* = 13.2, 8.4, 5.2 Hz, 1 H, C3-H), 0.86 (s, 6 H, C10-H), 0.47 (dd, *J* = 10.8, 5.2 Hz, 1 H, C3-H), 0.03 (s, 9 H, C12-H); ^{13}C NMR (100 MHz) δ 157.5 (C8), 139.3 (C5), 121.1 (C6), 115.9 (C9), 68.7 (C1), 62.8 (C7), 25.9 (C12), 21.2 (C4), 18.5 (C11), 18.3 (C2), 11.0 (C3), -5.3 (C10), -5.3 (C10).

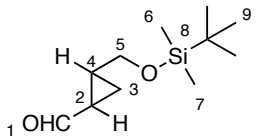


3.155a

(2-((*tert*-butyldimethylsilyloxy)methyl)cyclopropyl)methanol (3.155a). **(BLA-VII-166)**. Diiodomethane (629 mg, 0.19 mL, 2.34 mmol) was added to a solution of Et_2Zn (1.0 M in hexane, 1.28 mmol, 1.28 mL) in CH_2Cl_2 (4 mL) at 0 ˚C and stirred for 15 min. The resulting white slurry was cooled to –78 ˚C and a solution of **3.154** (216 mg, 1.06 mmol) in CH_2Cl_2 (2 mL) was added. The reaction was allowed to warm to 0 ˚C by

exchange of cooling baths and stirred for 1 h. The mixture was then allowed to warm to room temperature by removal of the cooling bath and stirring continued for 2 h. The reaction was cooled to 0 ˚C, saturated aqueous NH_4Cl (6 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 6 mL) and the combined organic fractions dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (2:1) to give 175 mg (81%) of **3.155a** as a clear, colorless oil: ^{1}H NMR (400 MHz) □ 3.60 (dd, *J* = 10.8, 5.6 Hz, 1 H), 3.45 (dd, *J* = 10.8, 6.4 Hz, 1 H), 3.52-3.42 (comp, 2 H), 1.38 (br s, 1 H), 1.07-0.98 (m, 1 H), 0.96-0.88 (m, 1 H), 0.89 (s, 9 H), 0.50 (ddd, *J* = 8.0, 4.8, 4.8 Hz, 1 H), 0.45 (ddd, *J* = 8.0, 5.2, 5.2 Hz, 1 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz) □ 66.0, 65.9, 25.9, 19.2, 19.1, 18.3, 7.6, -5.3, -5.3; IR ($CDCl_3$) 3612, 3417, 2955, 2883, 2858, 2247, 1471, 1256, 1077, 1006, 837 cm^{-1}; mass spectrum (CI) *m/z* 215.1465 [$C_{11}H_{23}O_2Si$ (M-1) requires 215.1467] 217, 199 (base).

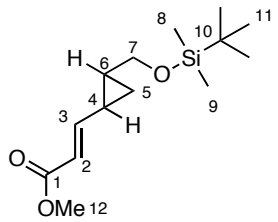
NMR Assignments: ^{1}H NMR (400 MHz) □ 3.60 (dd, *J* = 10.8, 5.6 Hz, 1 H, C5-H), 3.45 (dd, *J* = 10.8, 6.4 Hz, 1 H, C5-H), 3.52-3.42 (comp, 2 H, C1-H), 1.38 (br s, 1 H, O-H), 1.07-0.98 (m, 1 H), 0.96-0.88 (m, 1 H), 0.89 (s, 9 H, C5-H, C9-H), 0.50 (ddd, *J* = 8.0, 4.8, 4.8 Hz, 1 H, C3-H), 0.45 (ddd, *J* = 8.0, 5.2, 5.2 Hz, 1 H, C3-H), 0.05 (s, 6 H, C6-C7-H); ^{13}C NMR (100 MHz) □ 66.0 (C5), 65.9 (C1), 25.9 (C9), 19.2 (C4), 19.1 (C2), 18.3 (C8), 7.6 (C3), -5.3 (C6), -5.3 (C7).



3.156a

2-((*tert*-butyldimethylsilyloxy)methyl)cyclopropanecarbaldehyde (3.156a). (BLA-V-48). Dess-Martin periodinane (509 mg, 1.20 mmol) was added in one portion to a solution of **3.160** (130 mg, 0.60 mmol) in CH_2Cl_2 (6 mL) and stirred for 2 h at room temperature. Saturated aqueous $NaHCO_3/Na_2S_2O_3$ (6 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 6 mL) and the combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (2:1) to give 130 mg (quant.) of **3.156a** as a clear, colorless oil: ^{1}H NMR (400 MHz) 9.09 (d, *J* = 5.2 Hz, 1 H), 3.71 (dd, *J* = 10.4, 4.4 Hz, 1 H), 3.64 (dd, *J* = 10.4, 4.4 Hz, 1 H), 1.85 (app ddt, *J* = 9.6, 8.4, 4.4 Hz, 1 H), 1.73 (app ddt, *J* = 11.2, 9.2, 6.8, 4.8 Hz, 1 H), 1.27 (app dt, *J* = 8.8, 4.8, 4.8 Hz, 1 H), 1.13 (ddd, *J* = 11.2, 6.4, 4.4 Hz, 1 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz) 200.7, 62.5, 27.3, 25.7, 23.7, 18.2, 11.5, -5.5; IR ($CDCl_3$) 2956, 2858, 2256, 1703, 1471, 1258, 1098, 837 cm^{-1}; mass spectrum (CI) *m/z* 215.1470 [$C_{11}H_{23}O_2Si$ (M+1) requires 215.1467] 215 (base), 159.

NMR Assignments: ^{1}H NMR (400 MHz) 9.09 (d, *J* = 5.2 Hz, 1 H, C1-H), 3.71 (dd, *J* = 10.4, 4.4 Hz, 1 H, C5-H), 3.64 (dd, *J* = 10.4, 4.4 Hz, 1 H, C5-H), 1.85 (app ddt, *J* = 9.6, 8.4, 4.4 Hz, 1 H, C2-H), 1.73 (app ddt, *J* = 11.2, 9.2, 6.8, 4.8 Hz, 1 H, C3-H), 1.27 (app dt, *J* = 8.8, 4.8, 4.8 Hz, 1 H, C4-H), 1.13 (ddd, *J* = 11.2, 6.4, 4.4 Hz, 1 H, C3-H), 0.88 (s, 9 H, C9-H), 0.05 (s, 6 H, C6-C7-H); ^{13}C NMR (100 MHz) 200.7 (C1), 62.5 (C5), 27.3 (C2), 25.7 (C9), 23.7 (C4), 18.2 (C8), 11.5 (C3) –5.5 (C6-C7).

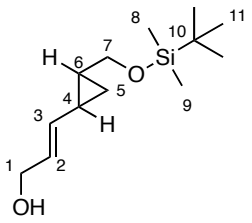


3.157a

(*E*)-Methyl 3-(2-((*tert*-butyldimethylsilyloxy)methyl)cyclopropyl)acrylate (3.157a). (BLA-VII-181). Trimethyl phosphonoacetate (257 mg, 1.4 mmol, 0.23 mL) was added to a slurry of NaH (54 mg of a 60% mineral oil suspension, 1.34 mmol) in THF (4 mL) at 0 ˚C and stirred for 1 h. A solution of **3.156a** (151 mg, 0.70 mmol) in THF (3 mL) was added, the reaction allowed to warm to room temperature by removal of the cooling bath and stirred for 1.5 h. H_2O (7 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 7 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1) to give 176 mg (93%) of **3.157a** as a clear, colorless oil: ^{1}H NMR (400 MHz) □ 6.49 (dd, *J* = 15.2, 10.0 Hz, 1 H), 5.86 (d, *J* = 15.2 Hz, 1 H), 3.71 (s, 3 H), 3.64 (dd, *J* = 11.2, 5.2 Hz, 1 H), 3.58 (dd, *J* = 11.2, 5.6 Hz, 1 H), 1.51 (app ddt, *J* = 10.0, 8.4, 4.4 Hz, 1 H), 1.30 (ddd, *J* = 8.8, 5.6, 4.0 Hz, 1 H), 0.94 (ddd, *J* = 10.8, 6.0, 4.8 Hz, 1 H), 0.88 (s, 9 H), 0.82 (app dt, *J* = 8.4, 4.8 Hz, 1 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz) □ 166.9, 152.9, 117.7, 64.2, 51.1, 25.8, 24.5, 19.3, 18.2, 12.8, -5.4; IR ($CDCl_3$) 3690, 2954, 2929, 2857, 2256, 1711, 1649, 1601, 1471, 1437, 1330, 1252, 1215, 1151, 1076 cm^{-1}; mass spectrum (CI) *m/z* 271.1743 [$C_{14}H_{27}O_3Si$ (M+1) requires 271.1730] 271 (base), 139.

NMR Assignments: ^{1}H NMR (400 MHz) □ 6.49 (dd, *J* = 15.2, 10.0 Hz, 1 H, C3-H), 5.86 (d, *J* = 15.2 Hz, 1 H, C2-H), 3.71 (s, 3 H, C12-H), 3.64 (dd, *J* = 11.2, 5.2 Hz, 1

H, C7-H), 3.58 (dd, *J* = 11.2, 5.6 Hz, 1 H, C7-H), 1.51 (app ddt, *J* = 10.0, 8.4, 4.4 Hz, 1 H, C5-H), 1.30 (ddd, *J* = 8.8, 5.6, 4.0 Hz, 1 H, C4-H), 0.94 (ddd, *J* = 10.8, 6.0, 4.8 Hz, 1 H, C5-H), 0.88 (s, 9 H, C11-H), 0.82 (app dt, *J* = 8.4, 4.8 Hz, 1 H, C6-H), 0.05 (s, 6 H, C8-C9-H); ^{13}C NMR (100 MHz) 166.9 (C1), 152.9 (C3), 117.7 (C2), 64.2 (C7), 51.1 (C12), 25.8 (C11), 24.5 (C4), 19.3 (C6), 18.2 (C10), 12.8 (C5), -5.4 (C8,C9).

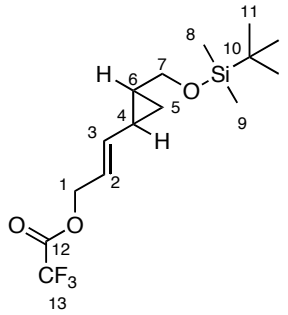


3.158a

(*E*)-3-(2-((*tert*-butyldimethylsilyloxy)methyl)cyclopropyl)prop-2-en-1-ol (3.158a). (BLA-VII-170). A 1.0 M solution of DIBALH in PhMe (0.93 mmol, 0.93 mL) was added to a solution of **3.157a** in THF (5 mL) at –78 ˚C. The reaction was allowed to warm to room temperature by removal of the cooling bath and stirred for 2 h. The mixture was then cooled to 0 ˚C, saturated Rochelle's salt (5 mL) was added and stirred for 30 min. The layers were separated and the aqueous phase extracted with EtOAc (3 x 5 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure to yield 110 mg (quant.) of **3.158a** as a clear colorless oil: ^{1}H NMR (400 MHz) 6.69 (app ddt, *J* = 15.2, 6.4, 0.8 Hz, 1 H), 5.29 (app ddt, *J* = 15.2, 8.8, 1.2 Hz, 1 H), 4.07 (dt, *J* = 7.2, 1.2 Hz, 1 H), 3.60 (dd, *J* = 10.8, 6.0 Hz, 1 H), 3.52 (dd, *J* = 10.8, 6.0 Hz, 1 H), 1.32 (app ddt, *J* = 12.8, 8.8, 4.4 Hz, 1 H), 1.21 (app t, *J* = 6.8 Hz, 1 H), 1.07 (app dddt, *J* = 12.4, 7.2, 5.6, 4.4 Hz, 1 H), 0.89 (s, 9 H), 0.69 (app dt, *J* = 8.4, 4.8 Hz, 1 H), 0.59 (app dt, *J* = 8.0, 4.8 Hz, 1 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz) 135.6,

126.7, 65.5, 63.4, 25.9, 22.7, 18.7, 18.3, 11.4, -5.2; IR ($CDCl_3$) 4195, 3605, 3053, 2956, 2857, 2305, 1666, 1421, 1260, 1074, 837, 766 cm^{-1}; mass spectrum (CI) *m/z* 243.1769 [$C_{13}H_{27}O_2Si$ (M+1) requires 243.1780] 243 (base), 241.

NMR Assignments: ^{1}H NMR (400 MHz) 6.69 (app ddt, *J* = 15.2, 6.4, 0.8 Hz, 1 H, C2-H), 5.29 (app ddt, *J* = 15.2, 8.8, 1.2 Hz, 1 H, C3-H), 4.07 (dt, *J* = 7.2, 1.2 Hz, 1 H, C1-H), 3.60 (dd, *J* = 10.8, 6.0 Hz, 1 H, C7-H), 3.52 (dd, *J* = 10.8, 6.0 Hz, 1 H, C7-H), 1.32 (app ddt, *J* = 12.8, 8.8, 4.4 Hz, 1 H, C5-H), 1.21 (app t, *J* = 6.8 Hz, 1 H, O-H), 1.07 (app dddt, *J* = 12.4, 7.2, 5.6, 4.4 Hz, 1 H, C5-H), 0.89 (s, 9 H, C11-H), 0.69 (app dt, *J* = 8.4, 4.8 Hz, 1 H, C6-H), 0.59 (app dt, *J* = 8.0, 4.8 Hz, 1 H, C4-H), 0.05 (s, 6 H, C8-C9-H); ^{13}C NMR (100 MHz) 135.6 (C3), 126.7 (C2), 65.5 (C7), 63.4 (C1), 25.9 (C11), 22.7 (C4), 18.7 (C6), 18.3 (C10), 11.4 (C5), -5.2 (C8-C9).



3.161

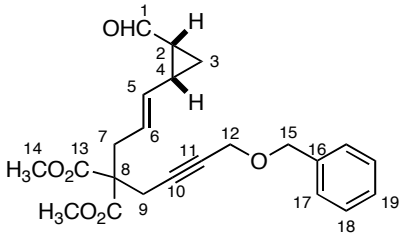
(*E*)-3-(2-((*tert*-butyldimethylsilyloxy)methyl)cyclopropyl)allyl 2,2,2-trifluoroacetate (3.161). **(BLA-VII-303)**. Trifluoroacetic anhydride (101 mg, 0.48 mmol, 0.07 mL) was added to a solution of **3.158a** (100 mg, 0.44 mmol) in Et_2O (2 mL) at 0 ˚C. The reaction was allowed to warm to room temperature by removal of the cooling bath and stirred for 15 min. Saturated aqueous $NaHCO_3$ (2 mL) was added and

the layers were separated. The aqueous phase was extracted with Et_2O (3 x 2 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure to provide 147 mg (99%) of **3.161** as a clear colorless oil: ^{1}H NMR (400 MHz) 5.65 (app dt, *J* = 15.6, 6.8 Hz, 1 H), 5.47 (dd, *J* = 15.6, 9.2 Hz, 1 H), 4.74 (d, *J* = 6.8 Hz, 2 H), 3.58 (d, *J* = 5.6 Hz, 2 H), 1.38 (app ddt, *J* = 13.2, 8.8, 4.4 Hz, 1 H), 1.12 (app ddt, *J* = 10.0, 5.6, 4.4 Hz, 1 H), 0.89 (s, 9 H), 0.78 (app dt, *J* = 8.4, 5.2 Hz, 1 H), 0.65 (app dt, *J* = 8.8, 4.4 Hz, 1 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz) 157.2, 142.7, 118.8, 115.9, 68.7, 65.1, 25.9, 23.2, 18.9, 18.4, 11.7, -5.2; IR ($CDCl_3$) 3690, 2956, 2929, 2857, 1781, 1601, 1471, 1223, 1173, 1149, 1089 cm^{-1}; mass spectrum (CI) *m/z* 339.1601 [$C_{15}H_{26}O_3F_3Si$ (M+1) requires 339.1603] 351, 339, 337 (base), 323, 309.

NMR Assignments: ^{1}H NMR (400 MHz) 5.65 (app dt, *J* = 15.6, 6.8 Hz, 1 H, C2-H), 5.47 (dd, *J* = 15.6, 9.2 Hz, 1 H, C3-H), 4.74 (d, *J* = 6.8 Hz, 2 H, C1-H), 3.58 (d, *J* = 5.6 Hz, 2 H, C7-H), 1.38 (app ddt, *J* = 13.2, 8.8, 4.4 Hz, 1 H), 1.12 (app ddt, *J* = 10.0, 5.6, 4.4 Hz, 1 H), 0.89 (s, 9 H, C11-H), 0.78 (app dt, *J* = 8.4, 5.2 Hz, 1 H, C5-H), 0.65 (app dt, *J* = 8.8, 4.4 Hz, 1 H, C5-H), 0.05 (s, 6 H, C8-C9-H); ^{13}C NMR (100 MHz) 157.2 (C12), 142.7 (C3), 118.8 (C2), 115.9 (C13), 68.7 (C7), 65.1 (C1), 25.9 (C11), 23.2 (C4), 18.9 (C10), 18.4 (C6), 11.7 (C5), -5.2 (C8,C9).

Procedure for the $[Rh(CO)_2Cl]_2$-Catalyzed Tandem Allylic Alkylation/[5+2] Cycloaddition of Allylic Trifluoroacetates 3.154, 3.159 and 3.161. The allylic trifluoroacetate (0.1 mmol) was added to a solution of $[Rh(CO)_2Cl]_2$ (5 mol%) in degassed MeCN (0.5 mL), and the solution stirred for 10 min at room temperature. In a separate flask, malonate **3.86** (1.5 mmol) was added to a slurry of NaH (60% w/w in mineral oil, 1.4 mmol) in degassed MeCN (0.5 mL) and stirred for 20 min at room

temperature. The resulting enolate solution was added *via* syringe to the solution of trifluoroacetate and $[Rh(CO)_2Cl]_2$ at room temperature. The mixture was then sealed in a screw cap vial under an atmosphere of argon, and stirring was continued at room temperature until the starting material was consumed (as indicated by TLC). The reaction was then heated to 80 °C (bath temperature) and stirring continued until intermediate enyne was consumed (as indicated by TLC). The reaction was then filtered through a short plug of silica gel eluting with Et_2O (50 mL), and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with pentane/Et_2O (5:1 or 10:1) to furnish the products **3.152**, **3.162** or **3.163**.



2.68a

Dimethyl 2-(4-(benzyloxy)but-2-ynyl)-2-((*E*)-3-((1*R*,2*R*)-2-formylcyclopropyl)allyl)malonate (2.68a) (BLA-III-244 and BLA-IV-233). $Pd(PPh_3)_4$ (170 mg, 0.15 mmol) and PPh_3 (281 mg, 1.07 mmol) were added in one portion each to a solution of **3.7** (211 mg, 1.52 mmol) in degassed THF (8 mL) and stirred for 20 min at room temperature. In a separate flask, **2.57** (887 mg, 3.06 mmol) was added to a mixture of NaH (92 mg of a 60% mineral oil suspension, 2.29 mmol) in degassed THF (8 mL) at room temperature and the mixture was stirred for 20 min. The resulting homogeneous

solution of malonate anion was transferred *via* cannula to the solution containing **3.7** and $Pd(PPh_3)_4$. The resulting mixture was heated under reflux and stirred for 4 h. The resulting dark brown solution was allowed to cool to room temperature, a saturated aqueous solution of $NaHSO_4$ (15 mL) was added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic fractions were washed with saturated aqueous NaCl (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (2:1 to 1:1) to give 440 mg (70%) of the carboxylic acid cyclopropyl enyne. Oxalyl chloride (0.18 mL, 2.06 mmol) was added to a solution of the carboxylic acid (440 mg, 1.03 mmol) and DMF (5 drops) in CH_2Cl_2 (10 mL) and stirred for 30 min at 0 ˚C. The reaction was allowed to warm to room temperature by removal of the cooling bath and stirred for 5 h. The mixture was then concentrated under reduced pressure and the crude acid chloride was dissolved in THF (7 mL) and cooled to –78 ˚C. A slurry of $LiAlH(O^tBu)_3$ (523 mg, 2.05 mmol) in THF (3 mL) was added and the reaction stirred for 4 h at –78 ˚C. An aqueous 1 M HCl (10 mL) solution was added at –78 ˚C and the mixture allowed to warm to room temperature by removal of the cooling bath. The layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 332 mg (81%) of **2.68a** as a clear, colorless oil: ^{1}H NMR (400 MHz) δ 9.30 (d, J = 4.8 Hz, 1 H), 7.36-7.29 (comp, 5 H), 5.56-5.53 (comp, 2 H), 4.56 (s, 2 H), 4.14 (t, J = 2.0 Hz, 2 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 2.84 (t, J = 2.0 Hz, 2 H), 2.78 (dd, J = 4.4, 2.4 Hz, 2 H), 2.13-2.06 (m, 2 H), 1.45 (app dt, J = 11.8, 5.2 Hz, 1 H), 1.37 (ddd, J = 11.8, 7.6, 5.2 Hz, 1 H); ^{13}C NMR (100 MHz) δ 200.6, 170.1, 137.4, 131.4, 128.4, 128.2, 126.1, 81.1, 79.3, 71.2, 57.3, 57.1, 52.7, 35.3,

29.8, 25.9, 23.1, 14.5; IR ($CDCl_3$) 3031, 2954, 2848, 2258, 1734, 1702, 1437, 1207, 1070 cm^{-1}; mass spectrum (CI) *m/z* 399.1799 [$C_{23}H_{27}O_6$ (M+1) requires 399.1807] 399 (base), 369, 307, 291, 241.

NMR Assignments: ^{1}H NMR (400 MHz) 9.30 (d, *J* = 4.8 Hz, 1 H, C1-H), 7.36-7.29 (comp, 5 H, C17-C18-C19-H), 5.56-5.53 (comp, 2 H, C5-C6-H), 4.56 (s, 2 H, C15-H), 4.14 (t, *J* = 2.0 Hz, 2 H, C12-H), 3.73 (s, 3 H, C14-H), 3.72 (s, 3 H, C14-H), 2.84 (t, *J* = 2.0 Hz, 2 H, C9-H), 2.78 (dd, *J* = 4.4, 2.4 Hz, 2 H, C7-H), 2.13-2.06 (m, 2 H, C2-C4-H), 1.45 (app dt, *J* = 11.8, 5.2 Hz, 1 H, C3-H), 1.37 (ddd, *J* = 11.8, 7.6, 5.2 Hz, 1 H, C3-H); ^{13}C NMR (100 MHz) 200.6 (C1), 170.1 (C13), 137.4 (C16), 131.4 (C5), 128.4, 128.2, 126.1 (C6), 81.1 (C10), 79.3 (C11), 71.2 (C15), 57.3 (C12), 57.1 (C8), 52.7 (C14), 35.3 (C7), 29.8 (C2), 25.9 (C4), 23.1 (C9), 14.5 (C3).

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